Supplementary material for "Discovery and Characterisation of 2-Aminooxazolines as Highly Potent, Selective and Orally Active TAAR1 Agonists"

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Biological assay section

Results were obtained from at least three independent experiments. Experiments were run at least in duplicates. EC_{50} values are given as a mean in nM. The E_{max} value for the functional activity data at TAAR1 receptor describes the degree of functional activity compared to 100% for the natural ligand and full agonist phenethylamine. Compounds with Emax<85% are regarded as partial agonists. The functional selectivity ratio of hTAAR1 vs. hα2A is determined by dividing the hα2A EC_{50} or IC_{50} value by the hTAAR1 EC_{50} value.

cAMP assay for determining functional activity at the human and rat TAAR1 receptor

Recombinant HEK293 cells expressing human, mouse or rat TAAR1 were grown at 37 °C and 5% CO_2 / 95% air in Falcon culture flasks in 30 ml culture medium. The cell culture medium contained DMEM high glucose, fetal calf serum (10%, non-dialysed, heat inactivated for 30 min at 56 °C), geneticin (375 µg/ml, Gibco), and penicillin/streptomycin (1%). Cells were harvested when 80 - 90% confluent. The culture medium was removed from the culture flasks and cells were washed once with 5 ml of PBS. After removing the PBS, 5 ml of trypsin/ EDTA solution were added for 5 min at 37 °C. Afterwards, 45 ml of culture medium was added to the 5 ml detached cell solution and the total of 50 ml was transferred into a Falcon tube. The tube was centrifuged at 900 rpm for 5 min at RT and the supernatant was removed. The cell pellet was resuspended in fresh culture medium and brought to 5 x 10 E5 cells per ml. Then the cells were plated in 96-well plates (BIOCOAT 6640, Becton Dickinson) with a multipipette (100 µl/ well, 50'000 cells/well) and incubated for 20 h at 37 °C.

Stimulation of the cells: The cell culture medium was removed, 100 µl PBS (AMIMED endotoxine free) was added and after 5 min under shaking at RT, PBS was removed and 90 µl PBS containing 1 mM IBMX was added. After shaking the cells for 2 min they were incubated for 10 min at 37 °C and 5% CO_2 / 95% air. All compounds were tested at a broad range of concentrations (100 pM to 10 µM) in duplicates. Typically, 10 µl of a compound solution in PBS and 1 mM IBMX or 10 µl of a 0.3 mM β-phenylethylamine solution (as maximal response) or 10 µl of a 2% DMSO solution (as basal level) were then added and after 10 min shaking the cells

were incubated for 30 min at 37 °C. Afterwards, the solutions were removed and the cells were lysed with 150 µl of lysis buffer (Millipore cAMP kit). The plates were then shaken for 30 min and stored at -20 °C.

cAMP Assay (Millipore cAMP kit): In the 96-well rabbit anti-cAMP antibody coated plates, 50 µl of cAMP standards (8 standards from 1 pmol/µl to 0.0039 pmol/µl and one without cAMP) or 50 µl of samples from the cell plates were added. A standard curve was performed on each plate. 25 µl of diluted cAMP alkaline phosphatase conjugated tracer was added to all wells followed by 50 µl of diluted rabbit anti-cAMP antibody. After sealing, the plates were incubated for 30 min at RT under shaking followed by removal of the supernatant from each well with an automated plate washer and by washing 5 times using 1 x wash buffer. Then, 100 µl of diluted alkaline phosphatase substrate was added, the plates sealed and incubated for 30 min at RT under shaking. Finally, the plates were read for 1 s with a luminometer (1420 Multilabel counter, PerkinElmer).

Assay for determining functional activity at the human adrenergic α2A receptor:
Membrane Preparation: CHL cells stably expressing the adrenergic α2A receptor were maintained at 37 °C and 5% CO_2 in DMEM high glucose medium containing fetal calf serum (5%, heat inactivated for 30 min at 56 °C) and 250 µg/ml geneticin (Gibco). Cells were released from culture flasks using trypsin/ EDTA, harvested, washed twice with ice-cold PBS (without Ca^{2+} and Mg^{2+}), pelleted at 1'000 rpm for 5 min at 4 °C, frozen and stored at -80 °C. Frozen pellets were suspended in 20 ml HEPES-NaOH (20 mM, pH 7.4) containing 10 mM EDTA and homogenized with a Polytron (PT 6000, Kinematica) at 14'000 rpm for 20 s. The homogenate was centrifuged at 48'000 x g for 30 min at 4 °C. Subsequently, the supernatant was removed and discarded, and the pellet resuspended in 20 ml HEPES-NaOH (20 mM, pH 7.4) containing 0.1 mM EDTA using the Polytron (20 s at 14'000 rpm). This procedure was repeated and the final pellet resuspended in HEPES-NaOH containing 0.1 mM EDTA and homogenized using the Polytron. Typically, aliquots of 2 ml membrane portions were stored at -80 °C.

Wheatgerm agglutinin SPA beads assay: The radioligand [^{35}S] GTPγS was used at a concentration of 0.5 nM final concentration. Nonspecific binding was defined as the amount of GTPγS bound in the presence of 10 µM final concentration of GTP (unlabeled ligand). Compounds were tested at a broad range of concentrations (30 pM to 30 µM) in duplicates. Norepinephrine was used as a reference for agonistic activity and RX821002 as an antagonist reference. A mix M was prepared containing GDP at 1.5 µM final concentration, membranes at 5 µg protein/well and wheatgerm agglutinin SPA beads at 1 mg/well. The test compounds (20 µl/well) were transferred into an OptiPlate (Perkin Elmer). 30 µl/well of buffer containing 50 mM Tris, 5 mM $MgCl_2$, 100 mM NaCl, 1 mM EDTA and 1 mM DTT were added. In order to determine the total binding 20 µl of buffer was used and for the nonspecific binding 20 µl of

GTP at 10 µM. For agonist testing 100 µl of mix M and 50 µl of [^{35}S] GTPγS were added. The OptiPlate was then incubated for 30 min at RT under shaking at 350 rpm/min and centrifuged for 3 min at 3000 rpm. Radioactivity was counted using a TopCount Microplate Scintillation Counter (Packard Instrument). For antagonist testing 100 µl of mix M and 50 µl of [^{35}S] GTPγS were added. The OptiPlate was then incubated for 5 min at RT under shaking at 350 rpm/min. 30 µl norepinephrine at 20 µM was added to the wells containing the compounds. The plate was then incubated for 25 min at RT under shaking at 350 rpm/min and centrifuged for 3 min at 3000 rpm. Radioactivity was counted using a TopCount Microplate Scintillation Counter (Packard Instrument). 50 µl of the ^{35}S-GTPγS stock were counted in 5 ml of ReadySafe scintillation cocktail (Beckman Industries) to determine the total counts added to the respective assays.

CEREP profiles

The full CEREP profiles of compounds **12**, **18**, **36** and **48** including a complete list of targets and radioligands used have already been published.

For compound **12** see: Revel et al "TAAR1 activation modulates monoaminergic neurotransmission, preventing hyperdopaminergic and hypoglutamatergic activity. Proc. Natl. Acad. Sci. U. S. A. 2011, 108, 8485-8490. Supplementary Material, pages 6-8 and is available at the publishers webpage http://dx.doi.org/10.1073/pnas.1103029108.

For compounds **18** and **48** see Revel et al "A New Perspective for Schizophrenia: TAAR1 Agonists Reveal Antipsychotic- and Antidepressant-like Activity, Improve Cognition, and Control Body Weight" Molecular Psychiatry (2013) 18, 543-556 Supplementary Material, pages 10-14 and is available at the publishers webpage http://www.nature.com/mp and http://dx.doi.org/10.1038/mp.2012.57.

For compound **36** see: Revel et al "Trace amine-associated receptor 1 partial agonism reveals novel paradigm for neuropsychiatric therapeutics. Biol. Psychiatry 2012, 72, 934-942. Supplementary Material, pages 13-17 and is available at the publishers webpage http://dx.doi.org/10.1016/j.biopsych.2012.05.014.

Drug metabolism section

All in vivo experiments were conducted in compliance with Swiss Federal and Cantonal laws on animal research and AAALAC regulations and received prior approval by the Cantonal Veterinary Office.

In vitro-characterisation of compound **12** (RO5166017) in mouse and rat liver microsomes

Species	**CL [ml/min/mg protein]**	**CL class**
Mouse	<10	low
Rat	259	high

Pharmacokinetic assessment of **12** (RO5166017) after i.v. and p.o. administration to mouse

Route	**i.v.**	**p.o.**
Dose (mg/kg)	2.5	10
Cmax (ng/mL)	251	4.7
Tmax (h)	0	0.25
AUC (ng/h per mL)	130	6.7
T1/2 (h)	0.77	1.8
Vss (L/kg)	5.8	
CL (mL/min per kg)	141	
F (%)		5.2
Fu (%)		25

Abbreviations: Cmax, maximum concentration; Tmax, time at which maximum concentration was observed; AUC, area under the plasma concentration vs. time curve; CL, clearance; Vss, volume of distribution at steady state; T1/2, terminal half-life; F, bioavailability; Fu, fraction unbound in plasma. Pharmacokinetic values are the mean of two animals per dose route.

In vitro-characterisation of compounds **29, 31, 33** and **36** in rat liver microsomes (RLM)

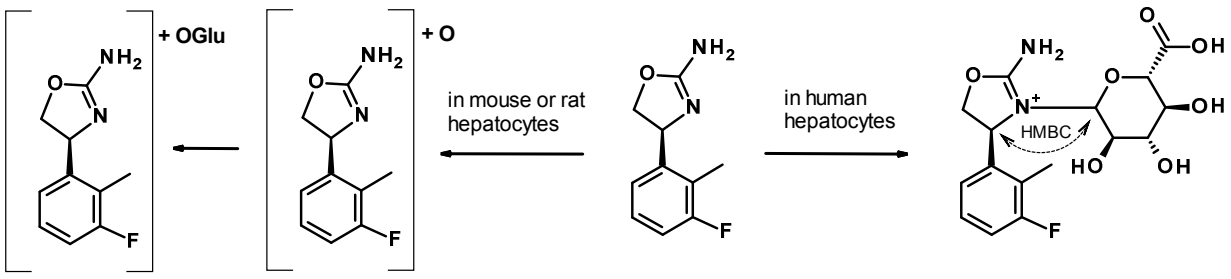
Compound	**CL RLM [ml/min/mg protein]**	**CL class**
29	876	high
31	925	high
32	87	med
36	<10	low

Comparison of in vitro clearance in rat liver microsomes (RLM) and in rat hepatocytes (Rhep) for compounds compounds **36,40, 46** and **48**

Compound	**CL RLM [ml/min/mg protein]**	**CL_m class**	**CL Rhep* [ml/min/kg]**	**CL_h class**
36	<10	low	1.1	low
40	<10	low	<1.0	low
46	15	med	3.2	low
48	<10	low	1.8	low

* the values are measured at 1 µM compound concentration

Metabolite ID confirmed different metabolic pathways for compound **48** (RO5263397) in mouse or rat vs. human hepatocytes



The N-glucuronide was isolated from a large scale incubation with human hepatocytes and its structure determined by ^{1}H- and ^{13}C-NMR spectroscopy including HMBC experiments.

Formation of Glutathione (GSH) adducts with selected compounds

Microsomal suspensions were diluted in 100 mM potassium phosphate buffer, pH7.4 to make 2 mg/ml solutions. One portion of this was heat denatured at 95 °C for 10 minutes, whilst the other remained on ice. The denatured protein solutions were then cooled before use.
Each incubation was made up using 220.5 µl of pretreated protein solution (see above, final concentration 1 mg/ml) and 4.5 µl substrate (final concentration 10 µM). This was warmed to 37 °C for 10 minutes before addition of 225 µl prewarmed glutathione solution in phosphate buffer (final concentration 5 mM). Incubations were stopped after 10 or 20 minutes incubation time (at 37 °C) by addition of 150 µl quench reagent (150:100:1 mix of 10% trichloroacetic acid : acetonitrile : 30% hydrogen peroxide). Samples were chilled on ice for 1 hour before centrifugation (20,000x g, 10 minutes). The supernatant was removed and 200 µl analysed by HPLC. Mass spectrometric analysis was performed on a LCQ mass spectrometer (Finnigan) equipped with the Xcalibur 1.2 software package.

Compound	**GSH-Adducts (MW)**	**GSH-Adduct (interpretation)**
12	M^1 = 540, M^2 = 540	M+GSH-2H+O, 2 isomers (o- and p-aminoquinone from aniline, then GSH addition)
40	none	
46	none	
47	M = 543	M+GSH, ring opening of aminooxazoline
48	M = 501	M+GSH, ring opening of aminooxazoline

Measurement of covalent binding using human hepatocytes

see literature:

Thompson, R. A.; Isin, E. M.; Li, Y.; Weaver, R.; Weidolf, L.; Wilson, I; Claesson, A.; Page, K.; Dolgos, H; Kenna, J. G. Risk assessment and mitigation strategies for reactive metabolites in drug discovery and development. *Chem. Bio. Int.* **2011**, *192*, 65-71.

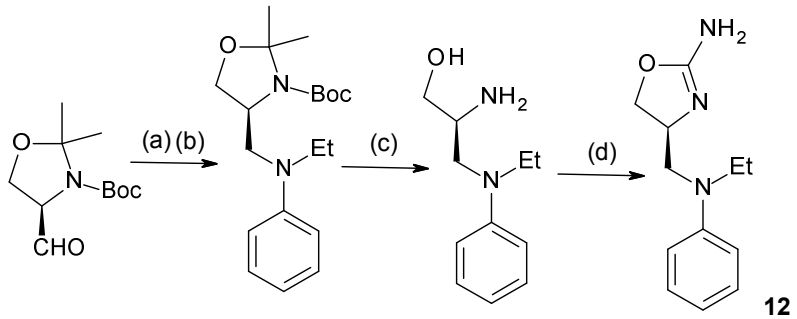
Usui, T.; Mise, M.; Hashizume, T.; Yabuki, M.; Komuro, S. Evaluation of the Potential for Drug-Induced Liver Injury Based on in Vitro Covalent Binding to Human Liver Proteins. *Drug Metabolism Disposition.* **2009**, *37*, 2383-2392.

Chemical synthesis section

Additional information regarding synthesis of compound **12** (RO5166017):

Compound **12** was prepared from Garner aldehyde according to the following scheme**:**

Synthesis of compound 12[a]



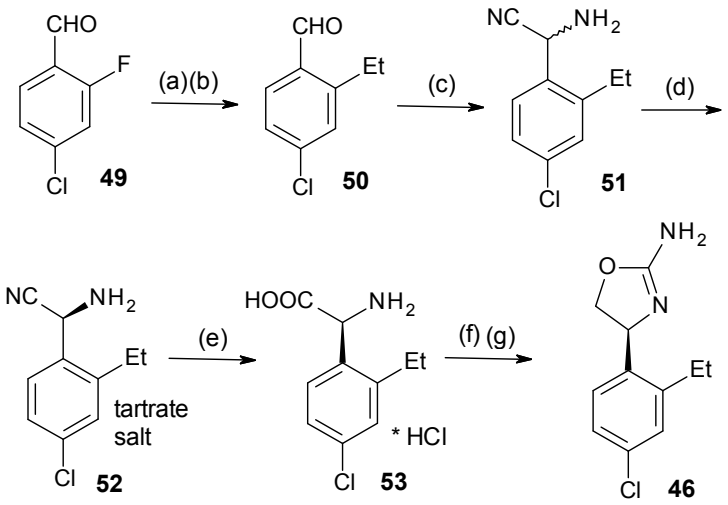
[a]Reagents and conditions: (a) aniline, $NaBH_3CN$, $ZnCl_2$, MeOH, 20-40 °C, 88% (b) EtCHO, $NaBH_3CN$, $ZnCl_2$, MeOH, 20-40 °C, 77% (c) i) 4 M HCl (in dioxane), dioxane, RT, ii) 1 N NaOH, H_2O, 84%; (d) BrCN, K_2CO_3, THF, RT, 53%.

Additional information regarding synthesis of compounds **32-48**

Compounds **32-48** were synthesised from phenylglycinols in a similar way to that described in the article, Scheme 1. In case the phenylglycine derivatives were not commercially available, a Strecker synthesis starting from the corresponding benzaldehyde was used. To access enantiomerically pure 2-amino-4-phenyloxazolines we either utilised chiral HPLC for separation at the final step, or we incorporated chiral amino acid derivatives in an earlier stage of the synthesis.

The following Scheme describes the access to the *o*-alkyl-*p*-chloro-derivatives **45-47** using the example of compound **46.** Benzaldehyde **49** was synthesised via fluorine-alkyl-exchange on the n-butylimine of **50**.We observed during optimisation of this cross-coupling reaction that no catalyst (such as $MnCl_2$) is needed when o-fluoro-benzaldehyde imines are used instead of o-chloro-benzaldehyde imines. In step d) the racemic Strecker product **51** was enantiomerically enriched by dynamic chiral resolution and recrystallisation to obtain the aminonitrile **52** in 92% ee as its tartrate salt. Subsequent nitrile hydrolysis by aqueous hydrochloric acid led to formation of the phenylglycine derivative **53** which was reduced and cyclised with cyanogen bromide to yield **46** in the final step.

Synthesis of 2-aminooxazoline 46 from 4-chloro-2-fluorobenzaldehyde[a]



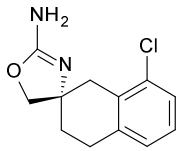
[a]Reagents and conditions: (a) n-BuNH_2, *p*-TsOH, toluene, 110 °C, 97%; (b) i) EtMgCl, THF, 0 °C, ii) 5 N aq. HCl, 100 °C, 98%; (c) TMSCN, 7 M aq. NH_3, MeOH, 0 °C-RT, 90%; (d) L-(+)-tartaric acid, acetone/MeOH/toluene, RT/40 °C/0 °C, 56% (92% ee); (e) 25% aq. HCl, 120 °C, 99% (f) $LiBH_4$, TMSCl, THF, RT, 60%; (g) K_2CO_3, BrCN, THF, 0 °C-RT, 63% (99% ee).

Chemistry experimental section

General Experimental

All solvents and reagents were obtained from commercial sources and were used as received. All reactions were followed by TLC (TLC plates F254, Merck) or LCMS (liquid chromatography-mass spectrometry) analysis. Proton and carbon NMR spectra were obtained on Bruker 300 or 600 MHz instrument with chemical shifts (δ in ppm) reported relative to tetramethylsilane as internal standard. NMR abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; br, broadened. Column chromatography was carried out on silica gel 60 (32-60 mesh, 60 A) or on prepacked columns (Isolute Flash Si, or Silicycle SiliaSep Amine). Mass spectra were recorded on an SSQ 7000 (Finnigan-MAT) spectrometer for electron impact ionization or an API150 (Applied Biosystems) using Turboionspray ESI Measurement of Optical Rotation was performed on an Anton Paar MCP 500 Polarimeter.High resolution mass spectrometric data (HRESI) were obtained on an Agilent Technologies (Santa Clara, California) Q-TOF spectrometer for electrospray ionization (ESI).

S18616 (1)

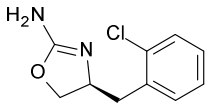


This compound was prepared as described in Eur. Pat. Appl. (1995), EP 635495.

General Procedure for the Formation of 2-Aminooxazolines from Amino Alcohols

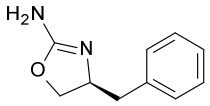
To a stirred solution of the amino alcohol (0.2 mmol) at 0 °C in 5 ml tetrahydrofuran was added dry potassium carbonate (0.24 mmol) followed by a solution of cyanogen bromide (0.24 mmol) in tetrahydrofuran (5 ml) in one portion. The ice bath was removed and stirring of the mixture was continued at room temperature for 90 min. For work-up the mixture was diluted with ethyl acetate (20 ml) and washed with water (20 ml). The aqueous phase was back extracted with ethyl acetate (20 ml). The combined organic layers were washed sequentially with water (20 ml) and brine (20 ml), dried (MgSO4), filtered and concentrated *in vacuo*. The residue was purified by chromatography (SiliaSep Amine column, 20 g, from Silicycle) using a gradient of 0 to 10% methanol in dichloromethane.

(S)-4-(2-Chloro-benzyl)-4,5-dihydro-oxazol-2-ylamine (2)



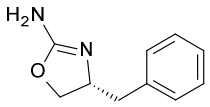
Compound **2** was prepared from (S)-2-amino-3-(2-chlorophenyl)propan-1-ol in 41% yield following the General Procedure. Light yellow oil. ^{1}H NMR (300 MHz, DMSO) δ 7.42-7.39 (m, 2H), 7.30-7.20 (m, 2H), 6.2 (br s, 2H), 4.23-4.14 (m, 2H), 3.91-3.83 (m, 1H), 2.87 (dd, J = 13.5, 6.3 Hz, 1H), 2.76 (dd, J = 13.5, 6 Hz, 1H). MS (ISP) m/e: 213.1 ([{^{37}Cl}M+H]$^{+}$), 211.1 ([{^{35}Cl}M+H]$^{+}$).

(S)-4-(2-Benzyl)-4,5-dihydro-oxazol-2-ylamine (3)



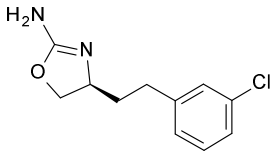
Compound **3** was prepared from (S)-2-amino-3-phenylpropan-1-ol in 66% yield following the General Procedure. White solid. ^{1}H NMR (300 MHz, DMSO) δ 7.29-7.19 (m, 4H), 7.19-7.15 (m, 1H), 5.80 (br s, 2H), 4.12-4.05 (m, 2H), 3.80-3.30 (m, 1H), 2.76 (dd, J = 13.7, 6 Hz, 1H), 2.58 (dd, J = 13.9, 6.6 Hz, 1H). MS (ISP) m/e: 177.1 (M+H^{+}).

(R)-4-(2-Benzyl)-4,5-dihydro-oxazol-2-ylamine (4)

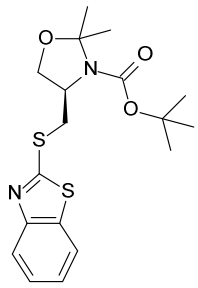


Compound **4** was prepared from (R)-2-amino-3-phenylpropan-1-ol in 54% yield following the General Procedure. Light yellow solid. ^{1}H NMR (300 MHz, DMSO) δ 7.29-7.19 (m, 4H), 7.19-7.14 (m, 1H), 5.83 (br s, 2H), 4.12-4.06 (m, 2H), 3.80-3.33 (m, 1H), 2.76 (dd, J = 13.7, 5.9 Hz, 1H), 2.58 (dd, J = 13.8, 6.6 Hz, 1H). MS (ISP) m/e: 177.1 (M+H^{+}).

(S)-4-[2-(3-Chloro-phenyl)-ethyl]-4,5-dihydro-oxazol-2-ylamine (5)

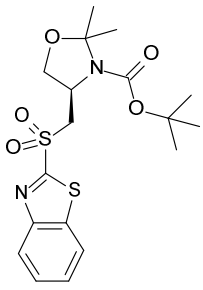


Step a: (R)-4-(Benzothiazol-2-ylsulfanyl-methyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester



To a stirred, cooled (0 °C) solution of (S)-4-hydroxymethyl-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (2.09 g, 9 mmol), 2-mercaptobenzothiazole (2.27 g, 13.5 mmol) and triphenylphosphine (3.55 g, 13.5 mmol) in THF (80 ml) under an argon atmosphere was added diethyl azodicarboxylate (5.9 ml, 13.5 mmol; 40 percent solution in toluene). The mixture (soon turning to a yellow suspension, slowly warming up to r.t.) was stirred for 18 h, then diluted with EtOAc and washed with sat. aq. Na_2CO_3. The aqueous phase was back extracted with EtOAc. The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2; gradient: cyclohexane to cyclohexane/EtOAc 85:15) to give (R)-4-(benzothiazol-2-ylsulfanyl-methyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (3.25 g, 94%) as a light yellow viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 7.5 Hz, 1H), 7.76 (dd, J = 7.8, 0.6 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 4.30 (br m, 1H), 4.09 (br d, J = 9.3 Hz, 1H), 4.00 (ddd, J = 9.6, 5.7, 1.2 Hz, 1H), 3.82 (br t, J = 13.8 Hz, 1H), 3.53-3.23 (br m, 1H), 1.64 (br d, J = 11.7 Hz, 3H), 1.51 (br s, 12H). MS (ISP) m/e: 381.0 ($M+H^+$).

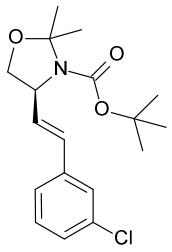
Step b: (R)-4-(Benzothiazole-2-sulfonylmethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester



To a stirred solution of (R)-4-(benzothiazol-2-ylsulfanyl-methyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (3.24 g, 8.52 mmol) at 0 °C in dichloromethane (100 ml) under an argon atmosphere was added 3-chloroperbenzoic acid (4.2 g, 17 mmol) in one portion. The mixture (slowly warming up to r.t.) was stirred overnight. The mixture was washed sequentially with 10% aq. sodium bisulfite (100 ml), sat. aq. Na_2CO_3 and brine, dried over $MgSO_4$, filtered

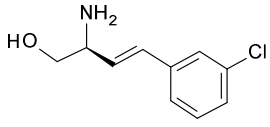
and concentrated *in vacuo*. The crude product was isolated by column chromatography (SiO_2; gradient: cyclohexane to cyclohexane/EtOAc 3:2) to give (R)-4-(benzothiazole-2-sulfonylmethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (1.64 g) an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, J = 7.5 Hz, 1H), 8.03 (d, J = 7.5 Hz, 1H), 7.64 (m, 2H), 4.55 (m, 1H), 4.34 (m, 1H), 4.07-3.75 (m, 2H), 3.68-3.54 (m, 1H), 1.58-1.44 (m, 6H), 1.29 (s, 9H). MS (ISP) m/e: 413.3 ($M+H^+$).

Step c: (S)-4-[(E)-2-(3-Chloro-phenyl)-vinyl-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester



To a stirred, cooled (0 °C) solution of 3-chlorobenzaldehyde (0.15 g, 1.04 mmol) in THF (10 ml) was added (R)-4-(benzothiazole-2-sulfonylmethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (0.512 g, 1.24 mmol) under an argon atmosphere. Then a 1 M solution of LiHMDS in THF (2.48 ml, 2.48 mmol) was added slowly. The mixture was stirred at 0 °C for 90 min and stirring was continued at r.t. overnight. The mixture was quenched by the addition of saturated aqueous NH_4Cl (15 ml) and H_2O (15 ml) and extracted twice with EtOAc. The aqueous phase was back extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2; gradient: heptane to heptane/EtOAc 70:30) to give (S)-4-[(E)-2-(4-fluoro-phenyl)-vinyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (0.35 g, 99%) as an off-white solid. ^{1}H NMR (300 MHz, DMSO) δ 7.55 (s, 1H), 7.41-7.28 (m, 3H), 6.45 (d, J = 15.9 Hz, 1H), 6.32 (dd, J = 14.4, 5.4 Hz, 1H), 4.40 (br s, 1H), 4.11-4.07 (m, 1H), 3.77 (dd, J = 8.1, 2.4 Hz, 1H), 1.57 (s, 3H), 1.46 (s, 3H), 1.34 (br s, 9H). MS (ISP) m/e: 340.2 ([{^{37}Cl}M+H]$^+$), 338.2 ([{^{35}Cl}M+H]$^+$).

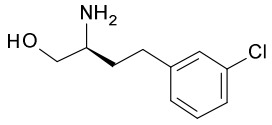
Step d: (E)-(S)-2-Amino-4-(3-chloro-phenyl)-but-3-en-1-ol



To (S)-4-[(E)-2-(4-fluoro-phenyl)-vinyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (350 mg, 1.05 mmol) was added 4 M HCl solution in dioxane (2.63 ml, 10.5 mmol) under

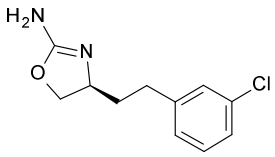
an argon atmosphere. The mixture was stirred for 16 h at r.t. The mixture was concentrated and a solution of sat. aq. Na_2CO_3 was added. The solution was extracted with EtOAc/THF 1:1 twice. The combined organics were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (SiliaSep Amine column, 20 g, gradient of 0 to 10% methanol in dichloromethane) to give (E)-(S)-2-amino-4-(3-chloro-phenyl)-but-3-en-1-ol (162 mg) as off-white solid. ^{1}H NMR (300 MHz, DMSO) δ 7.46 (s, 1H), 7.38-7.24 (m, 3H), 6.54 (d, J = 15.9 Hz, 1H), 6.35 (dd, J = 15.9, 5.4 Hz, 1H), 4.68 (br s, 1H), 3.44-3.24 (m, 3H), 1.60 (br s, 2H).

Step e: (S)-2-Amino-4-(3-chloro-phenyl)-butan-1-ol



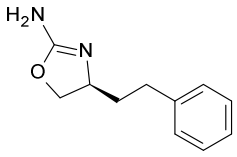
To a stirred solution of (E)-(S)-2-amino-4-(3-chloro-phenyl)-but-3-en-1-ol (0.155 g, 0.78 mmol) at r.t. in ethanol (5 ml) under an argon atmosphere was added the catalyst (5 % platinum on activated charcoal, 16 mg). The mixture was stirred at r.t. under a hydrogen atmosphere for 2 hrs. MS showed an incomplete reaction, therefore fresh catalyst (16 mg) was added and the mixture was stirred overnight under a hydrogen atmosphere. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give (S)-2-amino-4-(3-chloro-phenyl)-butan-1-ol (0.102 g) as a light yellow oil. ^{1}H NMR (300 MHz, DMSO) δ 7.32-7.16 (m, 4H), 4.48 (br s, 1H), 2.48-3.40 (m, 1H), 3.30-3.24 (m, 1H), 3.18-3.13 (m, 1H), 2.72-2.56 (m, 3H), 1.65-1.62 (m, 1H), 1.43-1.34 (m, 2H). MS (ISP) m/e: 202.2 ([{^{37}Cl}M+H]$^+$), 200.2 ([{^{35}Cl}M+H]$^+$).

Step f: (S)-4-[2-(3-Chloro-phenyl)-ethyl]-4,5-dihydro-oxazol-2-ylamine **(5)**



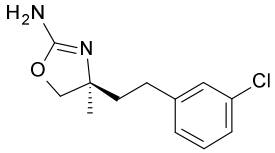
Compound **5** was prepared from (S)-2-amino-4-(3-chloro-phenyl)-butan-1-ol in 56% yield following the General Procedure. White solid. ^{1}H NMR (300 MHz, DMSO) δ 7.33-7.17 (m, 4H), 6.77 (br s, 2H), 4.33-4.29 (m, 1H), 3.91-3.83 (m, 2H), 2.73-2.56 (m, 2H), 1.72-1.65 (m, 2H). MS (ISP) m/e: 227.2 ([{^{37}Cl}M+H]$^+$), 225.1 ([{^{35}Cl}M+H]$^+$).

(S)-4-(2-Benzyl)-4,5-dihydro-oxazol-2-ylamine (6)

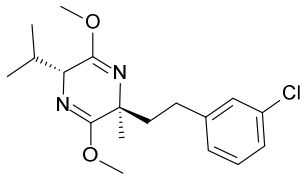


Compound **6** was prepared from (S)-2-amino-4-(3-chloro-phenyl)-butan-1-ol in 42% yield following the General Procedure. Off-white solid. ^{1}H NMR (300 MHz, DMSO) δ 7.29-7.16 (m, 5H), 5.84 (br s, 2H), 4.19 (t, J = 7.5 Hz, 1H), 3.82-3.70 (m, 2H), 2.69-2.45 (m, 2H), 1.63 (q, J = 7.8 Hz, 2H). MS (ISP) m/e: 191.3 ($M+H^+$).

(S)-4-[2-(3-Chloro-phenyl)-ethyl]-4-methyl-4,5-dihydro-oxazol-2-ylamine (7)

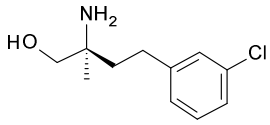


Step a: (2S,5R)-2-[2-(3-Chloro-phenyl)-ethyl]-5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydro-pyrazine



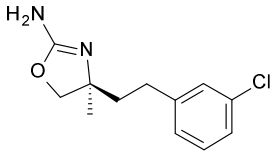
To a stirred solution of (2R,5SR)-(-)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-methylpyrazine (1.5 g, 7.57 mmol) in tetrahydrofuran (13 ml) at -70 °C was added slowly n-butyllithium solution (4.9 ml, 1.7M in pentane, 8.32 mmol) and stirring was continued at -70 °C for 1 h. A solution of 3-chlorophenethyl bromide (2.16 g, 9.84 mmol) in tetrahydrofuran (10 ml) was added slowly at this temperature. The cooling bath was removed and stirring was continued overnight. Ammonium chloride solution was added, and the mixture was extracted with ether three times. The combined organic layers were washed, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2; dichloromethane) to give (2S,5R)-2-[2-(3-chloro-phenyl)-ethyl]-5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydro-pyrazine (1.32 g, 52%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 6 Hz, 1H), 7.15 (d, J = 6 Hz, 2H), 7.08-7.13 (m, 1H), 4.02 (d, J = 3 Hz, 1H), 3.70 (d, J = 3 Hz, 6H), 2.32-2.46 (m, 1H), 2.46-2.56 (m, 1H), 2.28 (pd, 1H), 2.12 (td, 1H), 1.82 (td, 1H), 1.36 (s, 3H), 1.10 (d, J = 6 Hz, 3H), 0.71 (d, J = 6 Hz, 3H). MS (ISP) m/e: 337.2 ([{^{35}Cl}M+H]$^+$), 339.2 ([{^{37}Cl}M+H]$^+$).

Step b: (S)-2-amino-4-(3-chlorophenyl)-2-methyl-butan-1-ol



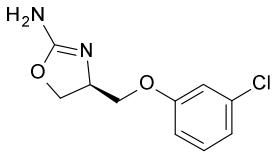
To a stirred solution of (2S,5R)-2-[2-(3-chloro-phenyl)-ethyl]-5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydro-pyrazine (1.3 g, 3.86 mmol) in a mixture of acetonitrile (15 ml) and water (5 ml) was added trifluoroacetic acid (2 ml). The mixture was stirred overnight at room temperature, then concentrated *in vacuo*. Saturated aq. $NaHCO_3$ solution was added and the mixture was extracted twice with dichloromethane. The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (SiliaSep Amine column, 20 g, gradient of 0 to 10% methanol in dichloromethane) to give 0.50 g of aminoester. For reduction this compound was dissolved in dry tetrahydrofuran (20 ml). Lithium aluminum hydride (117 mg, 3.09 mmol) was added and the mixture was stirred at room temperature overnight. Sodium sulfate (2 g) was added and the mixture was filtered through Speedex. The filtrate was concentrated *in vacuo* and the residue was purified by chromatography (SiliaSep Amine column, 20 g, gradient of 0 to 10% methanol in dichloromethane) to give 0.158 g of (S)-2-amino-4-(3-chlorophenyl)-2-methyl-butan-1-ol. Colourless oil. MS (ISP) m/e: 214.1 ([{^{35}Cl}M+H]$^+$), 216.1 ([{^{37}Cl}M+H]$^+$).

Step c: (S)-4-[2-(3-Chloro-phenyl)-ethyl]-4-methyl-4,5-dihydro-oxazol-2-ylamine

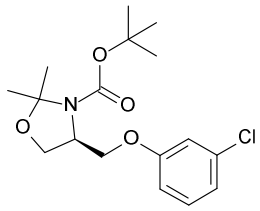


Compound **7** was prepared from (S)-2-amino-4-(3-chloro-phenyl)-2-methyl-butan-1-ol in 21% yield following the General Procedure. White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (dt, J1 = 7.5 Hz, J2 = 1.8 Hz, 1H), 7.12-7.22 (m, 3H), 4.18 (d, J = 8.1 Hz, 1H), 3.97 (d, J = 8.1 Hz, 1H), 3.9-4.5 (br s, 2H), 2.65-2.85 (m, 2H), 1.70-1.86 (m, 2H), 1.32 (s, 3H). MS (ISP) m/e: 239.1 ([{^{35}Cl}M+H]$^+$), 241.1 ([{^{37}Cl}M+H]$^+$).

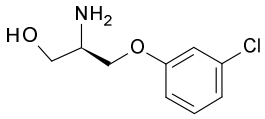
(S)-4-(3-Chloro-phenoxymethyl)-4,5-dihydro-oxazol-2-ylamine (8)



Step a: (S)-4-(3-Chloro-phenoxymethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester

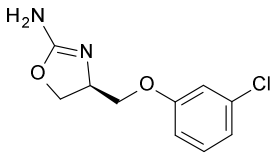


To a solution of (4S)-4-hydroxymethyl-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (0.5 g, 2.16 mmol) in tetrahydrofuran (10 ml) were added 3-chlorophenol (0.33 g, 2.59 mmol), triphenylphosphine (0.68 g, 2.59 mmol) and di-tert-butyl-azodicarboxylate (0.60 g, 2.59 mmol). The mixture was stirred at 60 °C for 20 hours. The solvent was evaporated and the residue was purified by column chromatography (SiliaSep Amine column, 50 g, gradient of 0 to 30% ethyl acetate in heptane) to give (S)-4-(3-chloro-phenoxymethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (462 mg) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22-7.16 (m, 1H), 6.93 (m, 2H), 6.86-6.81 (m, 1H), 4.16-4.00 (m, 4H), 3.85-3.82 (m, 1H), 1.63-1.47 (m, 15H).Step b: (R)-2-Amino-3-(3-chloro-phenoxy)-propan-1-ol



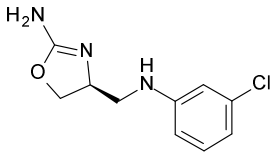
To (S)-4-(3-chloro-phenoxymethyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (462 mg, 1.35 mmol) in dioxane (5 ml) was added 4 M HCl solution in dioxane (6.75 ml, 17 mmol) under an argon atmosphere. The mixture was stirred at r.t. for 16 h. Then ethyl acetate (25 ml) and THF (25 ml) were added, and 2 N NaOH was used to bring the solution to pH=14. Saturated aq. sodium chloride solution was added and the organic layer was removed. It was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiliaSep Amine column, 20 g, gradient of 0 to 20% methanol in dichloromethane) to give (R)-2-amino-3-(3-chloro-phenoxy)-propan-1-ol (162 mg) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (t, J = 8 Hz, 1H), 6.96 (s, 1H), 6.93-6.91 (m, 1H), 6.80 (dd, J = 7.5, 2 Hz, 1H), 4.00-3.96 (m, 1H), 3.92-3.87 (m, 1H), 3.76-3.71 (m, 1H), 3.63-3.58 (m, 1H), 3.34-3.29 (m, 1H), 1.64 (br s, 3H), MS m/e: (ISP): 202.1 ({^{35}Cl} $[M+H]^+$),204.1 ({^{37}Cl} $[M+H]^+$).

Step c: (S)-4-(3-Chloro-phenoxymethyl)-4,5-dihydro-oxazol-2-ylamine

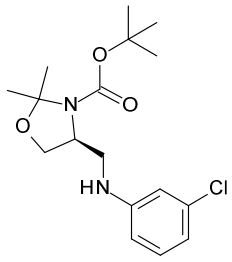


Compound **8** was prepared from (R)-2-amino-3-(3-chlorophenoxy)-propan-1-ol in 75% yield following the General Procedure. Colourless Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (t, J = 8 Hz, 1H), 6.93 (d, J = 8Hz, 1H), 6.91 (d, J = 2.4 Hz, 1H), 6.79 (dd, J = 8, 2.4 Hz, 1H), 4.44-4.41 (m, 4H), 4.25-4.24 (m, 1H), 4.08-4.03 (m, 1H), 3.87-3.84 (m, 1H), MS (ISP) m/e: 227.2 ([{^{35}Cl}M+H]$^+$), 229.2 ([{^{37}Cl}M+H]$^+$).

(S)-4-[(3-Chloro-phenylamino)-methyl]-4,5-dihydro-oxazol-2-ylamine (9)



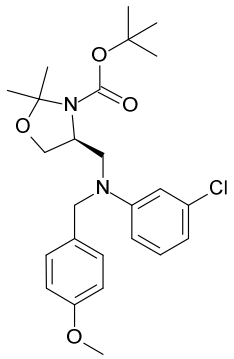
Step a: (S)-4-[(3-Chloro-phenylamino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester



To a stirred solution of tert-butyl (R)-(-)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate (0.83 g, 3.54 mmol) at r.t. in methanol (10 ml) under an argon atmosphere were added 3-chloroaniline (0.38 g, 2.95 mmol), $ZnCl_2$ (1.64 g, 11.8 mmol) and $NaBH_3CN$ (0.585 g, 8.85 mmol). The mixture was stirred at 40 °C for 3 h, then cooled to r.t. and concentrated *in vacuo* to leave a yellow paste. The crude product was purified by column chromatography (SiO_2; gradient of 0 to 30% ethyl acetate in heptane) to give (S)-4-[(3-chloro-phenylamino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (0.917 g, 91%) as an off-white solid. ^{1}H NMR (300 MHz, DMSO) δ 7.09-7.01 (m, 1H), 6.68-6.51 (m, 3H), 6.37-6.28 (m, 1H), 3.93-3.87 (m,

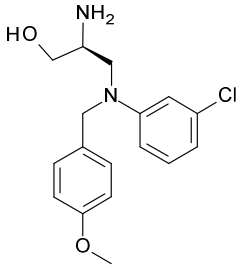
3H), 3.29-3.24 (m, 1H), 3.01-2.89 (m, 1H), 1.51-1.41 (m, 15H). MS (ISP) m/e: 343.2 ([{^{37}Cl}M^{+}H]$^{+}$), 341.1 ([{^{35}Cl}M^{+}H]$^{+}$).

Step b: (S)-4-{[(3-Chloro-phenyl)-(4-methoxy-benzyl)-amino]-methyl}-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester



To a stirred solution of (S)-4-[(3-chloro-phenylamino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (0.27 g, 0.79 mmol) at r.t. in 1,2-dichloroethane (10 ml) under an argon atmosphere were added p-methoxybenzaldehyde dimethyl acetal (0.22 g, 1.19 mmol), trifluoroacetic acid (0.06 ml, 0.79 mmol) and sodium triacetoxyborohydride (0.28 g, 1.19 mmol). The mixture was stirred at room temperature overnight. The mixture was directly adsorbed on silica gel and purified by chromatography (SiO_2; gradient of 0 to 30% ethyl acetate in heptane) to give (S)-4-{[(3-chloro-phenyl)-(4-methoxy-benzyl)-amino]-methyl}-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (0.36 g) as a white solid. ^{1}H NMR (300 MHz, DMSO) δ 7.15-7.06 (m, 3H), 6.89-6.60 (m, 5H), 4.69-4.61 (m, 1H), 4.53-4.47 (m, 1H), 4.20-4.15 (m, 1H), 3.95-3.87 (m, 1H), 3.80-3.77 (m, 1H), 3.71 (s, 3H), 3.67-3.54 (m, 1H), 3.45-3.36 (m, 1H), 1.54-1.51 (m, 3H), 1.44-1.39 (m, 12H). MS (ISP) m/e: 463.1 ([{^{37}Cl}M+H]$^{+}$), 461.1 ([{^{35}Cl}M+H]$^{+}$).

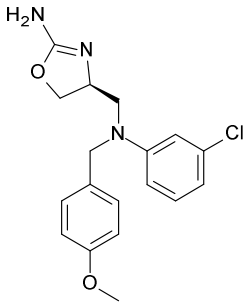
Step c: (S)-2-Amino-3-[(3-chloro-phenyl)-(4-methoxy-benzyl)-amino]-propan-1-ol



To (S)-4-{[(3-chloro-phenyl)-(4-methoxy-benzyl)-amino]-methyl}-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (0.36 g, 0.8 mmol) in dioxane (5 ml) was added 4 M HCl solution

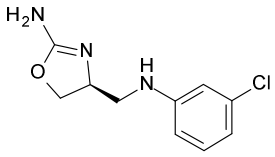
in dioxane (2.0 ml, 8 mmol) under an argon atmosphere. The mixture was stirred at r.t.for 16 h, then the solvent was evaporated. Saturated $NaHCO_3$ solution was added and the aqueous solution was extracted twice with a mixture of ethyl acetate and THF (1:1). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiliaSep Amine column, 20 g, gradient of 0 to 10% methanol in dichloromethane) to give (S)-2-amino-3-[(3-chloro-phenyl)-(4-methoxy-benzyl)-amino]-propan-1-ol (0.148 g) as a light yellow gum. ^{1}H NMR (300 MHz, DMSO) δ 7.10-7.05 (m, 3H), 6.87 (d, J = 8.7 Hz, 2H), 6.68-6.53 (m, 3H), 4.67 (br s, 1H), 4.58-4.50 (m, 2H), 3.71 (s, 3H), 3.50-3.20 (m, 4H), 3.03-2.95 (m, 1H), 1.50 (br s, 2H). MS (ISP) m/e: 323.3 ([{^{37}Cl}M^+H]$^+$), 321.2 ([{^{35}Cl}M^+H]$^+$).

Step d: (S)-4-{[(3-Chloro-phenyl)-(4-methoxy-benzyl)-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine



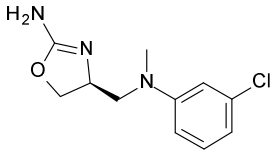
To a stirred solution of (S)-2-amino-3-[(3-chloro-phenyl)-(4-methoxy-benzyl)-amino]-propan-1-ol (0.14 g, 0.44 mmol) at 0 °C in 10 ml tetrahydrofuran was added dry potassium carbonate (0.07 g, 0.52 mmol) followed by a solution of cyanogen bromide (0.057 g, 0.52 mmol) in tetrahydrofuran (5 ml). The ice bath was removed and stirring of the mixture was continued overnight. The mixture was diluted with ethyl acetate (20 ml) and washed with water (20 ml). The aqueous phase was back extracted with ethyl acetate (20 ml). The combined organic layers were washed sequentially with water (20 ml) and brine (20 ml), dried (MgSO4), filtered and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, 20 g, gradient of 0 to 15% methanol in dichloromethane) to yield 0.097 g of a white solid. MS (ISP): 348.3 ([{^{37}Cl}M+H]$^+$), 346.1 ([{^{35}Cl}M+H]$^+$)

Step e: (S)-4-[(3-Chloro-phenylamino)-methyl]-4,5-dihydro-oxazol-2-ylamine

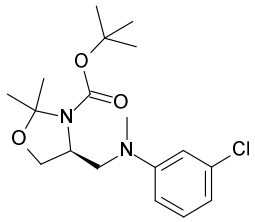


To a stirred solution of (S)-4-{[(3-chloro-phenyl)-(4-methoxy-benzyl)-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine (97 mg, 0.28 mmol) at r.t. in dichloromethane (10 ml) were added anisole (0.31 ml, 2.8 mmol) and trifluoroacetic acid (2.74 ml, 35 mmol). The mixture was stirred at r.t. for 48 h and was then concentrated *in vacuo*. The residue was partitioned between ethyl acetate and saturated aq. sodium bicarbonate solution, the phases were separated, and the organic phase was dried and concentrated *in vacuo*. The residue was purified by column chromatography (SiO2; gradient: gradient of 0 to 15% methanol in dichloromethane) to give (S)-4-[(3-chloro-phenylamino)-methyl]-4,5-dihydro-oxazol-2-ylamine (0.022 mg, 35%) as a white gum. ^{1}H NMR (300 MHz, DMSO) δ 7.05 (t, J = 8.1 Hz, 1H), 6.60 (1, 1H), 6.55-6.50 (m, 2H), 5.99 (br s, 2H), 5.88 (t, J = 5.6 Hz, 1H), 4.21 (t, J = 8.1 Hz, 1H), 4.07-3.98 (m, 1H), 3.88 (t, J = 6.9 Hz, 1H), 3.06-2.90 (m, 2H). MS (ISP) m/e: 228.1 ([{^{37}Cl}M+H]$^+$), 226.2 ([{^{35}Cl}M+H]$^+$).

(S)-4-{[(3-Chloro-phenyl)-methyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine (10)



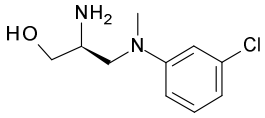
Step a: (S)-4-{[(3-Chloro-phenyl)-methyl-amino]-methyl}-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester



To a stirred solution of (S)-4-[(3-chloro-phenylamino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (0.25 g, 0.73 mmol; see Example 9, step a) at r.t. in methanol (10 ml) under an argon atmosphere were added formaldehyde (37% solution in H_2O; 0.28 ml, 3.67 mmol), zinc chloride (0.41 g, 2.9 mmol) and $NaBH_3CN$ (0.146 g, 2.2 mmol). The mixture was heated to 40 °C and stirring at that temperature was continued for 2 h. The mixture was concentrated and the residue was purified by column chromatography (SiO_2, 50 g, gradient of 0 to 30% ethyl acetate in heptane) to give (S)-4-{[(3-chloro-phenyl)-methyl-amino]-methyl}-2,2-

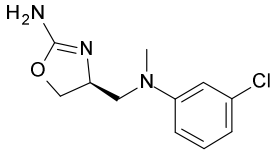
dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (0.24 g, 92%) as light yellow viscous oil. ^{1}H NMR (300 MHz, DMSO) δ 7.15 (t, J = 8.1 Hz, 1H), 6.80-6.63 (m, 3H), 4.15-4.04 (m, 1H), 3.94-3.85 (m, 1H), 3.79-3.72 (m, 1H), 3.57-3.20 (m, 2H), 2.96 (s, 3H), 1.56-1.51 (m, 3H), 1.42 (s, 12H). MS (ISP) m/e: 357.2 ([{^{37}Cl}M+H]$^+$), 355.2 ([{^{35}Cl}M+H]$^+$).

Step b: (S)-2-Amino-3-[(3-chloro-phenyl)-methyl-amino]-propan-1-ol



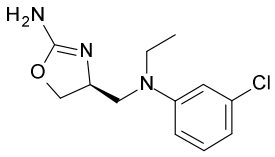
To (S)-4-{[(3-chloro-phenyl)-methyl-amino]-methyl}-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (0.23 g, 0.65 mmol) in dioxane (5 ml, 6.5 mmol) was added 4 M HCl solution in dioxane (1.6 ml) under an argon atmosphere. The mixture was stirred at r.t.for 16 h, then the solvent was evaporated. Saturated $NaHCO_3$ solution was added and the aqueous solution was extracted twice with a mixture of ethyl acetate and THF (1:1). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiliaSep Amine column, 20 g, gradient of 0 to 10% methanol in dichloromethane) to give (S)-2-amino-3-[(3-chloro-phenyl)-methyl-amino]-propan-1-ol (0.099 g) as a colourless oil. ^{1}H NMR (300 MHz, DMSO) δ 7.13 (t, J = 8 Hz, 1H), 6.67-6.62 (m, 2H), 6.57 (d, J = 8.1 Hz, 1H), 4.62 (br s, 1H), 3.35-3.22 (m, 3H), 3.15-3.07 (m, 1H), 2.97-2.89 (m, 1H), 2.92 (s, 3H), 1.45 (br s, 2H). MS (ISP) m/e: 217.2 ([{^{37}Cl}M+H]$^+$), 215.2 ([{^{35}Cl}M+H]$^+$).

Step c: (S)-4-{[(3-Chloro-phenyl)-methyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine

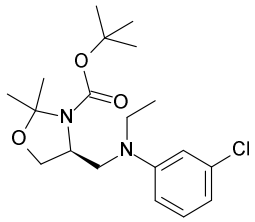


Compound **10** was prepared from (S)-2-amino-3-[(3-chloro-phenyl)-methyl-amino]-propan-1-ol in 47% yield following the General Procedure. Colourless gum. ^{1}H NMR (300 MHz, DMSO) δ 7.14 (t, J = 8.7 Hz, 1H), 6.64-6.65 (m, 2H), 6.60 (d, J = 7.2 Hz, 1H), 5.96 (br s, 2H), 4.20 (t, J = 7.8 Hz, 1H), 4.12-4.03 (m, 1H), 3.81 (t, J = 7.2 Hz, 1H), 3.34-3.29 (m, 2H), 2.93 (s, 3H). MS (ISP) m/e: 242.2 ([{^{37}Cl}M+H]$^+$), 240.1 ([{^{35}Cl}M+H]$^+$).

(S)-4-{[(3-Chloro-phenyl)-ethyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine (11)

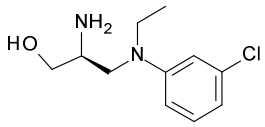


Step a: (S)-4-{[(3-Chloro-phenyl)-ethyl-amino]-methyl}-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester



To a stirred solution of (S)-4-[(3-chloro-phenylamino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (0.25 g, 0.73 mmol; see Example 9, step a) at r.t. in 1,2-dichloroethane (10 ml) under an argon atmosphere were added acetaldehyde (0.16 g, 3.67 mmol), sodium triacetoxyborohydride (0.52 g, 2.2 mmol) and acetic acid (0.04 ml, 0.73 mol). The mixture was shaken at 40 °C for 2 h. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (SiO_2, 50 g, gradient of 0 to 30% ethyl acetate in heptane) to give (S)-4-{[(3-chloro-phenyl)-ethyl-amino]-methyl}-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (0.22 g, 82%) as light yellow viscous oil. ^{1}H NMR (300 MHz, DMSO) δ 7.18-7.11 (m, 1H), 6.90-6.71 (m, 2H), 6.61 (d, J = 7.5 Hz, 1H), 4.15-4.04 (m, 1H), 3.93-.3.85 (m, 1H), 3.78-3.72 (m, 1H), 3.59-3.08 (m, 4H), 1.57-1.54 (m, 3H), 1.44-1.42 (m, 12H), 1.07-1.05 (m, 3H). MS (ISP) m/e: 371.2 ([{^{37}Cl}M+H]$^+$), 369.2 ([{^{35}Cl}M+H]$^+$).

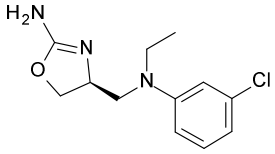
Step b: (S)-2-Amino-3-[(3-chloro-phenyl)-ethyl-amino]-propan-1-ol



To a solution of (S)-4-{[(3-chloro-phenyl)-ethyl-amino]-methyl}-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (0.22 g, 0.6 mmol) in dioxane (5 ml) was added 4 M HCl solution in dioxane (1.5 ml, 6 mmol) under an argon atmosphere. The mixture was stirred at r.t.for 16 h, then the solvent was evaporated. Saturated aq. $NaHCO_3$ solution was added and the aqueous solution was extracted twice with a mixture of ethyl acetate and THF (1:1). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiliaSep Amine column, 20 g, gradient of 0 to 10% methanol in dichloromethane) to give (S)-2-amino-3-[(3-chloro-phenyl)-ethyl-amino]-propan-1-

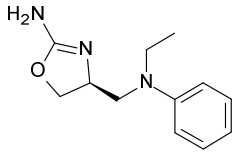
ol (0.125 g) as a colourless oil. ^{1}H NMR (300 MHz, DMSO) δ 7.11 (t, J = 8.1 Hz, 1H), 6.69-6.62 (m, 2H), 6.54 (dd, J = 7.8, 1.2 Hz, 1H), 4.63 (br s, 1H), 3.44-3.22 (m, 5H), 3.07-3.00 (m, 1H), 2.91-2.88 (m, 1H), 1.45 (br s, 2H), 1.04 (t, J = 6.9 Hz, 3H). MS (ISP) m/e: 231.1 ([{^{37}Cl}M+H]$^+$), 229.2 ([{^{35}Cl}M+H]$^+$).

Step c: (S)-4-{[(3-Chloro-phenyl)-ethyl-amino]-methyl}-4,5-dihydro-oxazol-2-ylamine

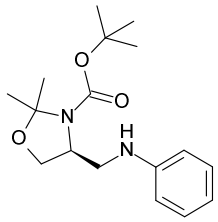


Compound **11** was prepared from (S)-2-amino-3-[(3-chloro-phenyl)-ethyl-amino]-propan-1-ol in 41% yield following the General Procedure. Colourless gum. ^{1}H NMR (300 MHz, DMSO) δ 7.12 (t, J = 8.1 Hz, 1H), 6.66-6.63 (m, 2H), 6.56 (d, J = 6.9 Hz, 1H), 5.99 (br s, 2H), 4.23 (t, J = 8.4 Hz, 1H), 4.09-4.04 (m, 1H), 3.83 (t, J = 7.2 Hz, 1H), 3.48-3.24 (m, 4H), 1.04 (t, J = 6.9 Hz, 3H). MS (ISP) m/e: 256.2 ([{^{37}Cl}M+H]$^+$), 254.1 ([{^{35}Cl}M+H]$^+$).

(S)-4-[(Ethyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine (12)



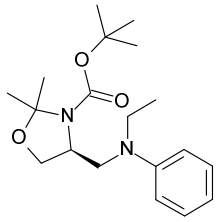
Step a: (S)-2,2-Dimethyl-4-phenylaminomethyl-oxazolidine-3-carboxylic acid tert-butyl ester



To a stirred solution of tert-butyl (R)-(-)-4-formyl-2,2-dimethyl-3-oxazolinecarboxylate (0.75 g, 3.27 mmol) at r.t. in methanol (20 ml) under an argon atmosphere were added aniline (0.277 g, 3 mol), $ZnCl_2$ (1.62 g, 12 mmmol) and $NaBH_3CN$ (0.561 g, 9 mmol). The mixture was stirred at r.t. for 18 h, then concentrated *in vacuo* to leave a yellow paste. The crude product was purified by column chromatography (SiO_2; gradient of 0 to 30% ethyl acetate in cyclohexane) to give (S)-2,2-Dimethyl-4-phenylaminomethyl-oxazolidine-3-carboxylic acid tert-butyl ester (0.75 g, 81%)

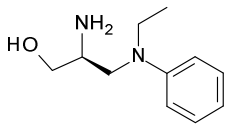
as an off-white solid. ^{1}H NMR (300 MHz,DMSO) δ 7.08-7.02 (m, 2H), 6.67-6.17 (m, 2H), 6.54-6.49 (m, 1H), 6.05-5.85 (m, 1H), 3.93-3.85 (m, 3H), , 3.30-3.25 (m, 1H), 2.94-2.91 (m, 1H), 1.52-1.37 (m, 15H). MS (ISP) m/e: 307.4 ($M+H^+$).

Step b: (S)-4-[(Ethyl-phenyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester



To a stirred solution of (S)-2,2-dimethyl-4-phenylaminomethyl-oxazolidine-3-carboxylic acid tert-butyl ester (0.74 g, 2.4 mmol) at r.t. in methanol (25 ml) under an argon atmosphere were added acetaldehyde (0.53 g, 12 mmol), sodium cyanoborohydride (0.45 g, 7 mmol) and zinc chloride (1.31 g, 9.6 mmol). The mixture was stirred at 40 °C for 18 h. The mixture was concentrated and the residue was purified by column chromatography (SiO_2, 50 g, gradient of 0 to 20% ethyl acetate in heptane) to give (S)-4-[(ethyl-phenyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (0.64 g, 80%) as a colourless amorphous compound. ^{1}H NMR (300 MHz, DMSO) δ 7.14-7.12 (m, 2H), 6.90-6.77 (m, 2H), 6.60 (t, J = 8.1 Hz, 1H), 4.11-4.08 (m, 1H), 3.95-3.82 (m, 1H), 3.81-3.71 (m, 1H), 3.52-3.35 (m, 2H), 3.35-3.05 (m, 2H), 1.57-1.53 (m, 3H), 1.46 (s, 9H), 1.42-1.40 (m, 3H), 1.06-1.02 (t, J = 6.7 Hz, 3H). MS (ISP) m/e: 335.6 ($M+H^+$).

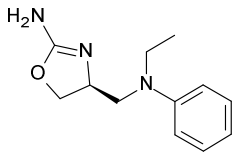
Step c: (S)-2-Amino-3-(ethyl-phenyl-amino)-propan-1-ol



To (S)-4-[(ethyl-phenyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (0.635 g, 1.9 mmol) in dioxane (5.2 ml, 19 mmol) was added 4 M HCl solution in dioxane (4.75 ml) under an argon atmosphere. The mixture was stirred at r.t.for 19 h, then the solvent was evaporated. 1 M aq. NaOH solution (10 ml) was added and the mixture was extracted twice with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiliaSep Amine column, 20 g, gradient of 0 to 10% methanol in dichloromethane) to give (S)-2-amino-3-(ethyl-phenyl-amino)-

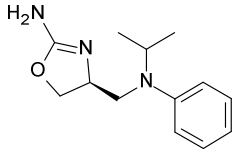
propan-1-ol (0.286 g) as a light yellow oil. ^{1}H NMR (300 MHz, DMSO) δ 7.12 (t, J = 7.2 Hz, 2H), 6.69 (d, J = 8.1 Hz, 2H), 6.53 (t, J = 7.2 Hz, 1H), 4.58 (br s, 1H), 3.43-3.2 (m, 5H), 3.06-2.89 (m, 2H), 1.43 (br s, 2H), 1.030 (t, J = 6.9 Hz, 3H). MS (ISP) m/e: 195.4 ($M+H^+$).

Step d: ((S)-4-[(Ethyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine

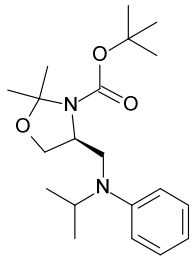


Compound **11** was prepared from (S)-2-amino-3-(ethyl-phenyl-amino)-propan-1-ol in 41% yield following the General Procedure. Light yellow gum. ^{1}H NMR (300 MHz, DMSO) δ 7.13 (t, J = 8.4 Hz, 2H), 6.68 (d, J = 8.7 Hz, 2H), 6.55 (t, J = 8.5 Hz, 1H), 5.87 (br s, 2H), 4.17 (t, J = 8.1 Hz, 1H), 4.15-4.02 (m, 1H), 3.83 (t, J = 7.5 Hz, 1H), 3.55-3.35 (m, 2H), 3.23 (d, J = 6 Hz, 2H), 1.04 (t, J = 6.6 Hz, 3H). MS (ISP) m/e: 220.3 ($M+H^+$).

(S)-4-[(Isopropyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine (13)



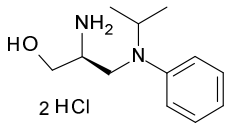
Step a: (S)-4-[(Isopropyl-phenyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester



To a stirred solution of (S)-2,2-dimethyl-4-phenylaminomethyl-oxazolidine-3-carboxylic acid tert-butyl ester (0.65 g, 2.1 mmol; see Example 12, step a) at r.t. in 1,2-dichloroethane (15 ml) under an argon atmosphere were added 2-methoxypropene (0.23 g, 3.2 mol), sodium triacetoxyborohydride (0.674 g, 3 mmol) and trifluoroacetic acid (0.16 ml, 2 mmol). The mixture was stirred at 40 °C for 18 h. The mixture was concentrated *in vacuo* and the residue was

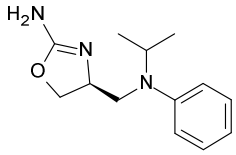
purified by column chromatography (SiO_2, 50 g, gradient of 0 to 30% ethyl acetate in heptane) to give (S)-4-[(Isopropyl-phenyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (0.66 g, 89%) as a light yellow viscous oil. ^{1}H NMR (300 MHz, DMSO) δ 7.16 (t, J = 6.2, 2H), 7.05 (d, J = 8.2 Hz, 1H), 6.97 (d, J = 8.3 Hz, 1H), 6.70 (t, J = 8.2 Hz, 1H), 4.05-3.98 (m, 2H), 3.82-3.76 (m, 2H), 3.25-3.18 (m, 1H), 2.98-2.83 (m, 1H), 1.60-1.57 (m, 3H), 1.49 (s, 6H), 1.46 (s, 3H), 1.41 (s, 3H), 1.12 (d, J = 6.6 Hz, 3H), 0.99 (m, 3H). MS (ISP) m/e: 349.5 ($M+H^+$).

Step b: (S)-2-Amino-3-(isopropyl-phenyl-amino)-propan-1-ol dihydrochloride



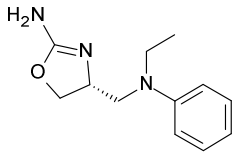
To (S)-4-[(isopropyl-phenyl-amino)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester (0.65 g, 1.86 mmol) in dioxane (5 ml) was added 4 M HCl solution in dioxane (9.3 ml, 37 mmol) under an argon atmosphere. The mixture was stirred at r.t.for 17 h, then the solvent was evaporated to give (S)-2-amino-3-(isopropyl-phenyl-amino)-propan-1-ol dihydrochloride (0.6 g) as a light brown foam. MS (ISP) m/e: 209.3 ($M+H^+$).

Step c: (S)-4-[(Isopropyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine



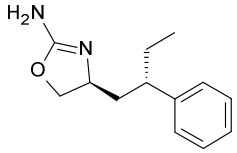
Compound **13** was prepared from (S)-2-amino-3-(isopropyl-phenyl-amino)-propan-1-ol dihydrochloride in 47% yield following the General Procedure. Light yellow gum. ^{1}H NMR (300 MHz, DMSO) δ 7.16 (t, J = 8.1 Hz, 2H), 6.77 (d, J = 8.7 Hz, 2H), 6.65 (t, J = 7.5 Hz, 1H), 5.87 (br s, 2H), 4.20-4.08 (m, 1H), 4.01-3.82 (m, 3H), 3.16 (dd, J = 14.7, 4.5 Hz, 1H), 3.00 (dd, J = 14.7, 6.6 Hz, 1H), 1.15 (d, J = 6.9 Hz, 3H), 1.04 (d, J = 6.6 Hz, 3H). MS (ISP) m/e: 234.3 ($M+H^+$).

(R)-4-[(Ethyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine (14)

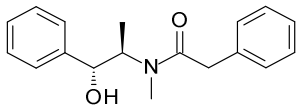


Compound **14** was prepared from tert-butyl (S)-(-)-4-formyl-2,2-dimethyl-3-oxazoline carboxylate instead of tert-butyl (R)-(-)-4-formyl-2,2-dimethyl-3-oxazoline carboxylate following the procedure for compound **12** (51%, Viscous oil. ^{1}H NMR (300 MHz, DMSO) δ 7.13 (t, J = 8.1 Hz, 2H), 6.68 (d, J = 8.4 Hz, 2H), 6.55 (t, J = 7.2 Hz, 1H), 5.88 (br s, 2H), 4.20 (t, J = 8.4 Hz, 1H), 4.07 (q, J = 6.3 Hz, 1H), 3.83 (t, J = 7.2 Hz, 1H), 3.50-3.30 (m, 2H), 3.23 (d, J = 6 Hz, 2H), 1.04 (t, J = 6.6 Hz, 3H). MS (ISP) m/e: 220.4 ($M+H^+$).

(S)-4-((S)-2-Phenyl-butyl)-4,5-dihydro-oxazol-2-ylamine (18)

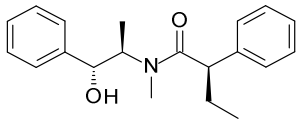


Step a: N-((1R,2R)-2-Hydroxy-1-methyl-2-phenyl-ethyl)-N-methyl-2-phenyl-acetamide (**21**)



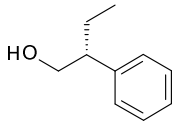
To a stirred solution of (-)-pseudoephedrine (10.8 g, 66 mmol) in dichloromethane (140 ml), was added triethylamine (11.8 ml, 85 mmol). Phenylacetyl chloride (10.8g, 70 mmol) in dichloromethane (30 ml) was added at 0-5 °C. The reaction mixture was stirred at r.t. for 16 h to give a white suspension. The reaction mixture was extracted with water. The organic layer was dried over Na_2SO_4, then concentrated *in vacuo*. The crude product was triturated with pentane, filtered through sintered glass to give *N*-((1R,2R)-2-hydroxy-1-methyl-2-phenyl-ethyl)-*N*-methyl-2-phenyl-acetamide (17.94 g, 96 %) as a white solid. ^{1}H NMR (13:5 rotamer ratio, asterisk denotes minor rotamer peaks, 300 MHz, $CDCl_3$) δ 7.33-7.16 (m, 10H), 4.62-4.59, (m 1H), 4.51* (d, J = 6.9 Hz, 1H), 4.48-4.40 (m, 1H), 4.24 (br s, 1H), 4.1-4.0* (m 1H), 3.84* (q, J = 13.5 Hz, 2H), 3.69 (s, 2H), 2.94* (s, 3H), 2.80 (s, 3H), 1.14 (d, J = 6.9 Hz, 3H), 0.81* (d, J = 6.9 Hz, 3H), MS (ISP) m/e: 284.2 ($M+H^+$).

Step b: (R)-N-((1R,2R)-2-Hydroxy-1-methyl-2-phenyl-ethyl)-N-methyl-2-phenyl-butyramide (**22**)



Lithium chloride (17 g, 63 mmol) was melted with a heat gun under vacuum. THF (70 ml) and diisopropylamine (20 ml, 141 mmol) were added. The reaction mixture was cooled to -78 °C (ethanol/dry ice). To this stirred solution was added a solution of butyllithium 1.6 M in hexane (82 ml, 131 mmol) below -65 °C. The reaction mixture was warmed to 0 °C then cooled to -78 °C to give a white suspension. *N*-((1R,2R)-2-Hydroxy-1-methyl-2-phenyl-ethyl)-*N*-methyl-2-phenyl-acetamide (17.8 g 63 mmol) in THF (110 ml) was added below -65 °C over 30 min. The reaction mixture was stirred at -78 °C for 1 h to give a yellow suspension. The reaction mixture was warmed to r.t., then cooled to 0 °C. Iodoethane (7.7 ml, 94 mmol) was added over 30 s. The reaction mixture was stirred at r.t. for 30 min to give a light yellow suspension. 25 ml sat. aq. NH_4Cl solution was added. The reaction mixture was poured into ethyl acetate, then 5 N aq. HCl was added to adjust the pH to pH 1. The organic layer was separated, dried over Na_2SO_4, then concentrated *in vacuo* to give (R)-N-((1R,2R)-2-hydroxy-1-methyl-2-phenyl-ethyl)-N-methyl-2-phenyl-butyramide (21.25 g 108 %) as yellow oil. ^{1}H NMR (8:3 rotamer ratio, asterisk denotes minor rotamer peaks, 300 MHz, $CDCl_3$) δ 7.38-7.2 (m, 10H), 4.59 (m, 2H), 4.37 (br s, 1H), 4.19-4.09* (m, 1H), 3.67-3.54* (m, 1H), 3.46 (t, J = 7.2 Hz, 1H), 2.91* (s, 3H), 2.69 (s, 3H), 2.11-2.01 (m, 1H), 1.76-1.66 (m, 1H), 1.56* (d, J = 6.3 Hz, 3H), 1.12 (d, J = 7.2 Hz, 3H), 0.89-0.81 (m, 3H), 0.497* (d, J = 6.3 Hz, 3H), MS (ISP) m/e: 312.1 ($M+H^+$).

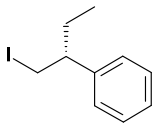
Step c: ((R)-1-Iodomethyl-propyl)-benzene (**23**)



To a stirred solution of diisopropylamine (40 ml, 282 mmol) in THF (120 ml) was added a solution of butyllithium 1.6 M in hexane (169 ml, 270 mmol) below -65 °C (ethanol/dry ice). The reaction mixture was warmed to 0 °C. Borane-ammonia complex (8.62 g, 251 mmol) was added in portions over 2 min (exotherm to 13 °C). The reaction mixture was stirred at 21 °C for 15 min, then cooled to 0 °C to give a white suspension. (R)-N-((1R,2R)-2-Hydroxy-1-methyl-2-phenyl-ethyl)-N-methyl-2-phenyl-butyramide (21.2 g, 63 mmol) in THF (130 ml) was added below 8 °C over 8 min. The reaction mixture was stirred at r.t. for 2.5 h then 15% aq. HCl (200 ml) was added dropwise to adjust the pH to pH 1. The reaction mixture was poured into ethyl acetate and extracted sequentially with water and saturated aq. NaCl solution. The organic layer was dried over Na_2SO_4 and then concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, dichloromethane/methanol) to give ((R)-1-iodomethyl-propyl)-benzene (8.07g, 85 %) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.2 (m, 5H), 3.80-3.69 (m,

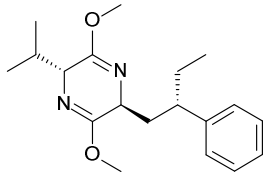
2H), 2.75-2.64 (m, 1H), 1.81-1.7 (m, 1H), 1.65-1.51 (m, 1H), 1.3-1.24 (m, 1H), 0.839 (t, J = 7.5 Hz, 3H), MS (EI): 150 M, chiral GC: 94 % ee, ret. time 12.82 min (FID, column BGB-174, 30 m x 0.25 mm, Nr. 12251133, 100-200 °C, run time 50 min).

Step d: ((R)-1-Iodomethyl-propyl)-benzene (**24**)



To a solution of triphenylphosphine (15.4 g, 59 mmol) and imidazole (3.99 g, 59 mmol) in dichloromethane (150 ml) at room temperature was added portionwise iodine (14.9 g, 50 mmol) at such a rate that the temperature of the reaction mixture did not rise above 30 °C. To the mixture was then added a solution of (R)-2-phenyl-butan-1-ol (7.34 g, 41 mmol, CAS 16460-75-6) in dichlorometahne (50 ml) and the mixture was then stirred at room temperature overnight. The mixture was then concentrated *in vacuo* and the residue was resuspended in ether and the resulting crystals were collected by filtration. The filtrate was concentrated *in vacuo* and the residue was triturated in heptane. The resulting crystals were removed by filtration and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, heptane/EtOAc) to yield a colourless oil, (6.38 g, 60 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.14 (m, 5H), 3.43-3.34 (m, 2H), 2.82-2.70 (m, 1H), 1.95-1.90 (m, 1H), 1.69-1.64 (m, 1H), 0.82 (t, J = 7.5 Hz, 3H), MS (EI) m/e: 260 (M).

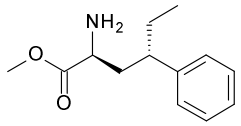
Step e: (2R,5S)-2-Isopropyl-3,6-dimethoxy-5-((S)-2-phenyl-butyl)-2,5-dihydro-pyrazine (**26**)



A solution of (R)-(-)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-pyrazine (4.25 g, 23.1 mmol) in tetrahydrofuran (30 ml) was cooled to -78 °C, then a solution of n-butyllithium (1.6 M in hexane, 15.1 ml, 24.2 mmol) was added and the mixture was stirred for 1 hour. A solution of ((R)-1-iodomethyl-propyl)-benzene (6.30 g, 24.2 mmol) in tetrahydrofuran (30 ml) was added dropwise over 30 min and the mixture was stirred overnight while being allowed to warm slowly from -70 °C to room temperature. The reaction was quenched by addition of saturated aqueous ammonium chloride solution and the mixture was extracted with ether. The organic layer was separated, washed with saturated brine, then dried over Na_2SO_4 and concentrated *in vacuo*. The

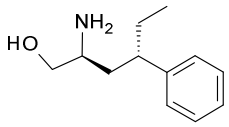
residue was purified by column chromatography (SiO_2, heptane/EtOAc) to yield a light yellow oil (4.69 g, 64%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.10 (m, 5H), 3.98-4.02 (m, 1H), 3.76 (t, J = 3.6 Hz, 1H), 3.69 (s, 3H), 3.69 (m 1H) 3.44 (s, 3H), 2.78-2.69 (m, 1H), 2.27-2.1 (m, 2H), 2.04-1.95 (m, 1H), 1.70-1.50 (m, 1H), 0.97 (d, J = 6.6 Hz, 3H), 0.76 (t, J = 6.6 Hz, 3H, 0.65 (d, J = 6.9 Hz, 3H), MS (ISP) m/e: 317.2 ($M+H^+$).

Step f: (2S,4S)-2-Amino-4-phenyl-hexanoic acid methyl ester (**27**)



To a solution of trifluoroacetic acid (3.4 ml) in water (440 ml) was added dropwise over 15 min a solution of (2R,5S)-2-isopropyl-3,6-dimethoxy-5-((S)-2-phenyl-butyl)-2,5-dihydro-pyrazine (4.69 g, 14.8 mmol) in acetonitrile (75 ml). The mixture was stirred at room temperature overnight then made basic by addition of saturated aqueous sodium carbonate solution and the mixture was extracted with ethyl acetate. The phases were separated and the organic phase was washed sequentially with water and with saturated brine, then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, EtOAc/heptane) to yield a yellow oil (2.78 g, 85 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.18 (m, 5H), 3.64 (s, 3H), 3.11 (dd, J = 12, 3.5 Hz, 1H), 2.12-2.01 (m, 1H), 1.82-1.72 (m, 1H), 1.69-1.59 (m, 2H), 1.46 (s, 3H), 0.78 (t, J = 9 Hz, 3H), MS (ISP) m/e: 222.3 ($M+H^+$).

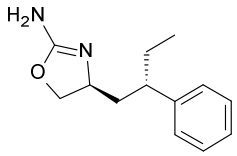
Step g: (2S,4S)-2-Amino-4-phenyl-hexan-1-ol (**28**)



To a suspension of lithium aluminum hydride (121 mg, 3.18 mmol) in tetrahydrofuran (8 ml) was added a solution of (2S,4S)-2-amino-4-phenyl-hexanoic acid methyl ester (320 mg, 1.45 mmol) in tetrahydrofuran (10 ml) and the mixture was stirred for 16 hours. The reaction was quenched by dropwise addition of ethyl acetate, then acidified to pH 5 by addition of hydrochloric acid and then made basic by addition of saturated aqueous sodium bicarbonate solution. The mixture was taken up in ethyl acetate/tetrahydrofuran (1:1), the phases were separated and the organic phase was washed sequentially with water and with saturated brine. The organic phase was then dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography (column: Isolute® Flash-NH_2 from Separtis; eluent:

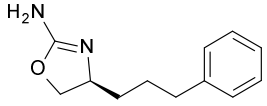
dichloromethane/MeOH) to yield a yellow oil, (116 mg, 42 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.14 (m, 5H), 3.56 (dd, J = 7.2, 3.6 Hz, 1H), 3.26 (dd, J = 10.8, 7.5 Hz, 1H), 2.77-2.68 (m, 1H), 2.55-2.46 (m, 1H), 2.10 (br s, 3H), 1.80-1.49 (m, 4H), 0.75 (t, J = 4.5 Hz, 3H), MS (ISP) m/e: 194.3 ($[M+H]^+$), chiral GC: 98 % ee, ret. time 43.69 min (FID, column BGB-174, 30 m x 0.25 mm, Nr. 13011628, 100-200 °C, run time 60 min).

Step h: (S)-4-((S)-2-Phenyl-butyl)-4,5-dihydro-oxazol-2-ylamine (**18**)



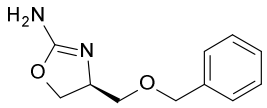
To a stirred, cooled (0 °C) solution of (2S,4S)-2-amino-4-phenyl-hexan-1-ol (270 mg, 1.40 mmol) and sodium acetate (229 mg, 2.70 mmol) in methanol (20 ml) was added dropwise a solution of cyanogen bromide (180 mg, 1.68 mmol) in methanol (2 ml) over 10 min. The mixture was then allowed to warm to r.t. and stirring was continued for 16 h. The mixture was concentrated *in vacuo* and the residue was taken up in ethyl acetate and washed sequentially with saturated aqueous sodium bicarbonate solution and with saturated brine. The organic phase was dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by chromatography (column: Isolute® Flash-NH_2 from Separtis; eluent: heptane/EtOAc/MeOH) to yield a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.12 (m, 5H), 4.30 (br s, 2H), 4.26 (t, J = 7.5 Hz, 1H), 3.88-3.78 (m, 2H), 2.52-2.42 (m, 1H), 2.03-1.94 (m 1H), 1.78-1.1.69 (m, 2H), 1.62-1.52 (m, 1H), 0.77 (t, J = 7.4 Hz, 3H), ^{13}C NMR (300 MHz, CDCl3) 160.49, 144.83, 128.43, 127.62, 126.18, 73.12, 61.99, 44.60, 43.26, 29.55, 12.04, $[\alpha]^{20}_D$ + 19.35° (c = 1.00, MeOH), MS (ISP) m/e: 219.3 ($[M+H]^+$). 99 % ee chiral HPLC (column Chiralpak-IC, 25cm x 4.6 mm, heptane/ethanol + 0.2 % ethylenediamine; ret. time 7.49 min.) HRESI calcuated for C13H18N2O $[M]^+$ m/z 218.14191; measured m/z 218.14321.

(S)-4-(3-Phenyl-propyl)-4,5-dihydro-oxazol-2-ylamine (29)



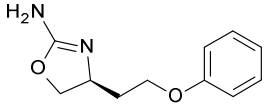
Compound **29** was prepared following the procedure for compound **18** using (3-bromo-propyl)-benzene instead of ((R)-1-iodomethyl-propyl)-benzene in step e). Yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$)) δ 7.29-7.25 (m, 5H), 4.33 (t, J = 7.8 Hz, 1H), 4.01-3.96 (m, 1H) 3.84 (t, J = 7.5 Hz, 1H), 3.72-3.65 (m, 1H), 3.6-3.4 (m, 1H), 2.05-2.01 (m, 2H),1.59 (m, 4H), MS (ISP) m/e: 205.1 ($M+H^+$).

(S)-4-Benzyloxymethyl-4,5-dihydro-oxazol-2-ylamine (30)

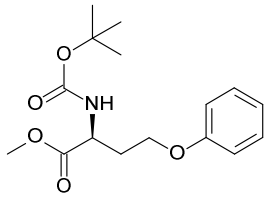


Compound **30** was prepared from (R)-2-amino-3-benzyloxypropan-1-ol in 29% yield following the General Procedure. Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.40 (m, 5H), 4.55 (s, 2H), 4.34 (t, J = 7.2 Hz, 1H), 4.09-4.25 (m, 2H), 4.0-4.5 (br s, 2H), 3.58 (dd, J1 = 9.3 Hz, J2 = 4.2 Hz, 1H), 3.38 (dd, J1 = 9.3 Hz, J2 = 2.4 Hz, 1H), MS (ISP) m/e: 206.9 ($M+H^+$).

(S)-4-(2-Phenoxy-ethyl)-4,5-dihydro-oxazol-2-ylamine (31)

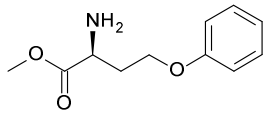


Step a: (S)-2-tert-Butoxycarbonylamino-4-phenoxy-butyric acid methyl ester



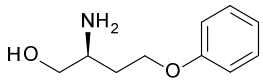
To a stirred solution of (S)-(tert-butoxycarbonylamino)-4-hydroxybutyric acid methyl ester (1.43 g, 6.1 mmol) in THF (4 ml) were added phenol (692 mg, 7.36 mmol), triphenylphosphine (1.77 g, 6.74 mmol) and diisopropyl azodicarboxylate (1.36 g, 6.74 mmol). The resulting yellow solution was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography (SiO2; gradient: heptane/EtOAc 100:0 to 90:10) to give (S)-2-tert-butoxycarbonylamino-4-phenoxy-butyric acid methyl ester (1.16 g, 61 %) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.25 (m, 2H), 6.95 (t, J = 6 Hz, 1H), 6.86 (d, J = 6 Hz, 2H), 5.3 (br s, 1H), 4.05 (t, J = 6 Hz, 2H), 3.76 (s, 3H), 2.30 (m, 2H), 1.44 (s, 9H), MS (ISP) m/e: 210.1 ($[M+H-BOC]^+$)).

Step b: (S)-2-Amino-4-phenoxy-butyric acid methyl ester



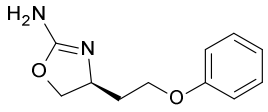
To a solution of (S)-2-tert-butoxycarbonylamino-4-phenoxy-butyric acid methyl ester (1.15 g, 3.72 mmol) in dichloromethane (3 ml) was added under an argon atmosphere trifluoroacetic acid (4.2 ml, 37.2 mmol). The mixture was stirred for 16 h. The mixture was concentrated. The residue was treated with sodium bicarbonate solution until the pH was basic and extracted twice with dichloromethane. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The product, a yellow oil, was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.25 (m, 2H), 6.98-6.88 (m, 3H), 4.14-4.11 (m, 2H), 3.74-3.70 (m, 4H), 2.33-2.20 (m, 1H), 2.05-1.93 (m, 1H), 1.64 (br s, 2H); MS (ISP) m/e: 210.3 ($[M+H]^+$)).

Step c: (S)-2-Amino-4-phenoxy-butan-1-ol



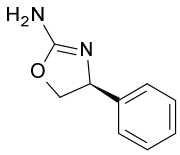
To a suspension of lithium aluminum hydride (282 mg, 7.4 mmol) in tetrahydrofuran (4 ml) was added a solution of (S)-2-amino-4-phenoxy-butyric acid methyl ester (778 mg, 3.7 mmol) in tetrahydrofuran (3 ml) and the mixture was stirred at 50 °C for 2 hours. Sodium hydroxide solution (4N) was added until gas evolution ceased and the suspension was filtered through Celite. The solvent was evaporated and the residue was purified by chromatography (column: Isolute® Flash-NH2 from Separtis; eluent: ethyl acetate/ MeOH = 98:2) to yield a colourless oil, (180 mg, 27 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2H), 6.95 (t, J = 7 Hz, 1H), 6.90 (d, J = 7 Hz, 1H) 4.1 (t, J = 6 Hz, 2H), 3.64 (dd, J = 10.5, 3.9 Hz, 1H), 3.4 (dd, J = 10.5, 7.2 Hz, 3H), 3.14 (m, 1H), 1.94 (m, 1H), 1.79 (m, 1H), 1.77(br s, 2H); MS (ISP) m/e: 182.3 ($(M+H)^+$.).

Step d: (S)-4-(2-Phenoxy-ethyl)-4,5-dihydro-oxazol-2-ylamine



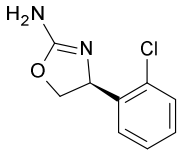
To a stirred mixture of (S)-2-amino-4-phenoxy-butan-1-ol (175 mg, 0.97 mmol) and K_2CO_3 (200 mg, 1.45 mmol) in THF (5 ml) under an argon atmosphere was added a solution of cyanogen bromide (123 mg, 1.16 mmol) in THF (1 ml). The mixture was stirred for 18 hours, then water and ethyl acetate were added. The organic layer was washed with water, dried over $MgSO_4$ and concentrated *in vacuo* over Isolute® Flash-NH_2 silica gel. Chromatography (column: Isolute® Flash-NH_2 from Separtis; eluent: ethyl acetate/ MeOH = 95:5) yielded the title compound as a white solid, (62 mg, 31 %); ^{1}H NMR (300 MHz, $CDCl_3$)) δ 7.30-7.25 (m, 2H), 6.95 (t, J = 7.5 Hz, 1H), 6.89 (d, J = 8.4 Hz, 2H) 4.45 (t, J = 8.1 Hz, 1H), 4.25-4.16 (m, 1H), 4.13-4.01 (m, 3H), 2.05-2.01 (m, 2H),1.59 (br s, 2H), MS (ISP) m/e: 207.1 ($(M+H)^+$.).

(S)-4-Phenyl-4,5-dihydro-oxazol-2-ylamine (32)



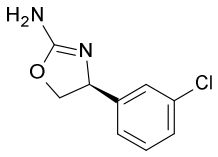
Compound **32** was prepared from (L)-(+)-phenylglycinol in 40% yield following the General Procedure. White solid. ^{1}H NMR (300 MHz, DMSO) δ 7.34-7.20 (m, 5H), 6.06 (br s, 2H), 4.95 (t, J = 8.8 Hz, 1H), 4.52 (t, J = 7.6 Hz, 1H), 3.78 (t, J = 7.6 Hz, 1H). MS (ISP) m/e: 163.3 ($M+H^+$).

(S)-4-(2-Chloro-phenyl)-4,5-dihydro-oxazol-2-ylamine (33)



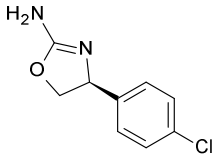
Compound **33** was prepared from (R)-2-amino-2-(2-chloro-phenyl)-ethanol in 36% yield following the General Procedure. Light yellow solid. ^{1}H NMR (300 MHz, DMSO) δ 7.47-7.26 (m, 4H), 6.20 (br s, 2H), 5.20 (dd, J = 9.3, 6.9 Hz, 1H), 4.64 (dd, J = 9.3, 8.1 Hz, 1H), 3.76 (dd, J = 7.8, 6.9 Hz, 1H). MS (ISP) m/e: 199.3 ([{^{37}Cl}M+H]$^+$), 197.3 ([{^{35}Cl}M+H]$^+$).

(S)-4-(3-Chloro-phenyl)-4,5-dihydro-oxazol-2-ylamine (34)



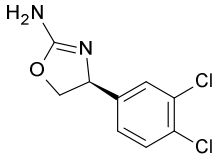
Compound **34** was prepared from (R)-2-amino-2-(3-chloro-phenyl)-ethanol in 31% yield following the General Procedure. Light yellow solid. ^{1}H NMR (300 MHz, DMSO) δ 7.39-7.30 (m, 3H), 7.21 (d, J = 7.2 Hz, 1H), 6.23 (br s, 2H), 4.99 (t, J = 8 Hz, 1H), 4.53 (t, J = 8.6 Hz, 1H), 3.82 (t, J = 7.5 Hz, 1H). MS (ISP) m/e: 199.0 ([{^{37}Cl}M+H]$^{+}$), 197.0 ([{^{35}Cl}M+H]$^{+}$).

(S)-4-(4-Chloro-phenyl)-4,5-dihydro-oxazol-2-ylamine (35)



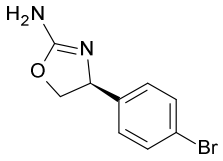
Compound **35** was prepared from (R)-2-amino-2-(4-chloro-phenyl)-ethanol in 53% yield following the General Procedure. Light yellow solid. ^{1}H NMR (300 MHz, DMSO) δ 7.37 (dd, J = 6.3 Hz, 1.8 Hz, 2H), 7.27 (dd, J = 6.9, 1.8 Hz, 2H), 6.10 (br s, 2H), 4.96 (dd, J = 9, 7.2 Hz, 1H), 4.51 (dd, J = 9, 7.8 Hz, 1H), 3.77 (dd, J = 7.8, 7.2 Hz, 1H). MS (ISP) m/e: 199.1 ([{^{37}Cl}M+H]$^{+}$), 197.1 ([{^{35}Cl}M+H]$^{+}$).

(S)-4-(3,4-Dichloro-phenyl)-4,5-dihydro-oxazol-2-ylamine (36)



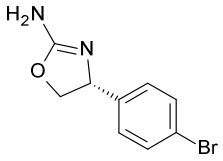
Compound **36** was prepared by reaction of rac-2-amino-2-(3,4-dichloro-phenyl)-ethanol with cyanogen bromide in 46% yield according to the General Procedure, followed by chiral column chromatography (Chiralpak AD, EtOH/heptane = 20:80) to give an off-white solid, (+)-enantiomer. ^{1}H NMR (300 MHz, DMSO) δ 7.59 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 1.8 Hz, 1H), 7.24 (dd, J = 8.4, 1.8 Hz, 1H), 6.21 (br s, 2H), 4.99 (dd, J = 9, 6.9 Hz, 1H), 4.52 (dd, J = 9, 8.1 Hz, 1H), 3.81 (dd, J = 8.1, 7.2 Hz, 1H). MS (ISP) m/e: 233.1 ([{^{37}Cl}M+H]$^{+}$), 231.1 ([{^{35}Cl}M+H]$^{+}$). HRESI calcuated for C9H8Cl2N2O [M]$^{+}$ m/z 230.00137; measured m/z 230.00213.

(S)-4-(4-Bromo-phenyl)-4,5-dihydro-oxazol-2-ylamine (37)



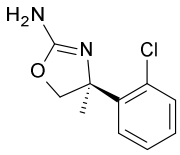
Compound **37** was prepared by reaction of rac-2-amino-2-(4-bromo-phenyl)-ethanol with cyanogen bromide in 60% yield according to the General Procedure, followed by chiral column chromatography (Chiralpak AD, EtOH/heptane = 20:80) to give an off-white solid, (+)-enantiomer. Retention time 14.14 min. Chiralpak AD. 1ml/min, 25bar, heptane/ethanol 8:2. ^{1}H NMR (300 MHz, DMSO) δ 7.52 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 6.44 (br s, 2H), 4.97 (t, J = 9 Hz, 1H), 4.55 (t, J = 8.1 Hz, 1H), 3.82 (t, J = 7.5 Hz, 1H). MS (ISP) m/e: 241.1 ([{^{79}Br}M+H]$^{+}$), 243.1 ([{^{81}Br}M+H]$^{+}$).

(R)-4-(4-Bromo-phenyl)-4,5-dihydro-oxazol-2-ylamine (38)

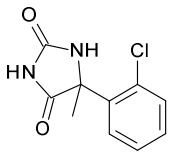


Compound **38**was prepared by reaction of rac-2-amino-2-(4-bromo-phenyl)-ethanol with cyanogen bromide in 60% yield according to the General Procedure, followed by chiral column chromatography (Chiralpak AD, EtOH/heptane = 20:80) to give an off-white solid, (-)-enantiomer. (-)-Enantiomer. Retention time 8.09 min. Chiralpak AD. 1ml/min, 25bar, heptane/ethanol 8:2. ^{1}H NMR (300 MHz, DMSO) δ 7.52 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 6.44 (br s, 2H), 4.98 (dd, J = 9, 7.2 Hz, 1H), 4.56 (t, J = 8.1 Hz, 1H), 3.83 (t, J = 7.2 Hz, 1H). MS (ISP) m/e: 241.1 ([{^{79}Br}M+H]$^{+}$), 243.1 ([{^{81}Br}M+H]$^{+}$).

(S)-4-(2-Chloro-phenyl)-4-methyl-4,5-dihydro-oxazol-2-ylamine (39)

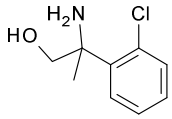


Step a: 5-(2-Chloro-phenyl)-5-methyl-imidazolidine-2,4-dione



A solution of 2-chloroacetophenone (5.0 g, 32 mmol) in ethanol/water 1:1 (80 ml) was treated under an argon atmosphere with ammonium carbonate (15.5 g, 162 mmol) and sodium cyanide (1.9 g, 39 mmol). The mixture was heated at 60 °C for 3 h. It was cooled to 0 °C and the solution was brought to acidic pH by dropwise addition of 3 N aq. hydrochloric acid (120 ml). Then nitrogen was bubbled through the solution for 1 h to remove remaining HCN. Ethanol and part of of the water were removed by distillation. The remaining aqueous solution was extracted with ethyl acetate. The crude product was purified by column chromatography (SiO_2, 50 g, gradient of 0 to 70% ethyl acetate in cyclohexane) to give 5-(2-chloro-phenyl)-5-methyl-imidazolidine-2,4-dione (1.4 g, 19%) as white solid. ^{1}H NMR (300 MHz, DMSO) δ 10.85 (br s, 1H), 8.23 (s, 1H), 7.66-7.63 (m, 1H), 7.50-7.46 (m, 1H), 7.42-7.39 (m, 2H), 1.75 (s, 3H). (ISP) m/e: 227.3 ([{^{37}Cl}M+H]$^+$), 225.3 ([{^{35}Cl}M+H]$^+$).

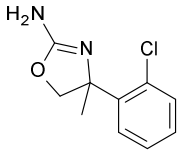
Step b: 2-Amino-2-(2-chloro-phenyl)-propan-1-ol



A mixture of 5-(2-chloro-phenyl)-5-methyl-imidazolidine-2,4-dione (1.4 g, 6 mmol) and aqueous sodium hydroxide solution (4M, 18.7 ml, 75 mmol) was stirred at 120 °C for 4 h. It was cooled to 0 °C and the solution was brought to pH=1 by dropwise addition of hydrochloric acid (25% in water). Water was evaporated to yield a solid which was dried carefully *in vacuo*. The residue was suspended in tetrahydrofuran (20 ml) under argon atmosphere. After cooling the mixture to 0 °C, lithium aluminum hydride (0.45 g, 12 mmol) was added slowly and the mixture was then stirred at room temperature for 20 h. The mixture was cooled to 0 °C, then tetrahydrofuran (5 ml) and water (0.5 ml) were added (caution!). Aq. sodium hydroxide solution (4 N, 0.5 ml) and water (1.5 ml) were added and the mixture was stirred at room temperature for 30 min. The mixture was filtered and the solid was washed with THF. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography (Isolute® Flash-NH_2 from Separtis, 50 g, gradient of 0 to 5% methanol in dichloromethane) to give 2-amino-2-(2-chloro-phenyl)-propan-1-ol (0.313 g, 28%) as light yellow solid. ^{1}H NMR (300 MHz, DMSO) δ 7.78 (dd, J = 7.8, 1.8 Hz, 1H), 7.36-7.19 (m, 3H),

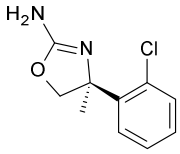
4.73 (t, J = 5.7 Hz, 1H), 3.81 (dd, J = 10.5, 5.7 Hz, 1H), 3.64 (dd, J = 10.5, 5.7 Hz, 1H), 2.01 (br s, 2H), 1.42 (s, 3H). MS (ISP) m/e: 188.3 ([{^{37}Cl}M+H]$^+$), 186.3 ([{^{35}Cl}M+H]$^+$).

Step c: 4-(2-Chloro-phenyl)-4-methyl-4,5-dihydro-oxazol-2-ylamine



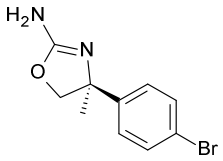
To a stirred mixture of 2-amino-2-(2-chloro-phenyl)-propan-1-ol (313 mg, 1.69 mmol) and K_2CO_3 (279 mg) in THF (3 ml) under an argon atmosphere was added a solution of cyanogen bromide (214 mg, 2 mmol) in THF (3 ml). The mixture was stirred for 18 hours, then water and ethyl acetate were added. The organic layer was washed with water, dried over $MgSO_4$ and concentrated *in vacuo* over Isolute® Flash-NH_2 silica gel. Chromatography (column: Isolute® Flash-NH_2 from Separtis; 20 g, gradient of 0 to 10% methanol in dichloromethane) yielded the title compound as a white solid, (235 mg, 66 %); ^{1}H NMR (300 MHz, DMSO) δ 7.91 (dd, J = 7.8, 2.1 Hz, 1H), 7.40 (dd, J = 7.5, 1.5 Hz, 1H), 7.33-7.22 (m, 2H), 6.04 (br s, 2H), 4.49 (d, J = 8.4 Hz, 1H), 4.14 (d, J = 8.1 Hz, 1H), 1.46 (s, 3H). MS (ISP) m/e: 213.1 ([{^{37}Cl}M+H]$^+$), 211.1 ([{^{35}Cl}M+H]$^+$).

Step d: (S)-4-(2-Chloro-phenyl)-4-methyl-4,5-dihydro-oxazol-2-ylamine

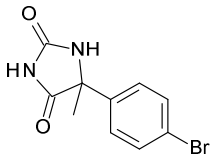


The enantiomers were separated by preparative chiral HPLC using a Chiralpak AD column and 10% EtOH/Heptane as eluent (flow 1 ml/min, 25 bar). The title compound is the (+)-enantiomer and has a retention time of 7.58 min (the (-)-enantiomer has a retention time of 5.63 min). White solid. ^{1}H NMR (300 MHz, DMSO) δ 7.91 (dd, J = 7.5, 2.1 Hz, 1H), 7.40 (dd, J = 7.5, 1.5 Hz, 1H), 7.33-7.22 (m, 2H), 6.04 (br s, 2H), 4.49 (d, J = 8.4 Hz, 1H), 4.14 (d, J = 8.4 Hz, 1H), 1.46 (s, 3H). MS (ISP) m/e: 213.1 ([{^{37}Cl}M+H]$^+$), 210.9 ([{^{35}Cl}M+H]$^+$).

(S)-4-(4-Bromo-phenyl)-4-methyl-4,5-dihydro-oxazol-2-ylamine (40)

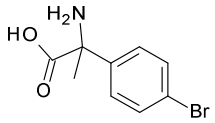


Step a: 5-(4-Bromo-phenyl)-5-methyl-imidazolidine-2,4-dione



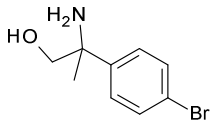
A solution of 4-bromoacetophenone (20.0 g, 100 mmol) in ethanol (100 ml) was treated under an argon atmosphere with water (100 ml), ammonium carbonate (48.27 g, 500 mmol) and sodium cyanide (5.9 g, 121 mmol). The mixture was heated at 60 °C for 16 h. It was then cooled to 0 °C and the solution was brought to acidic pH by dropwise addition of 3 N aq. hydrochloric acid. Then nitrogen was bubbled through the solution for 1 h to remove remaining HCN. The solid was collected by filtration and washed with water and dichloromethane to give 5-(4-bromo-phenyl)-5-methyl-imidazolidine-2,4-dione (23.34 g, 86%) as a white solid. ^{1}H NMR (300 MHz, DMSO) δ 10.8 (br s, 1H), 8.64 (s, 1H), 7.60 (d, J = 9 Hz, 2H), 7.42 (d, J = 9 Hz, 2H), 1.63 (s, 3H). MS (ISP) m/e: 266.8 ([{^{79}Br}M+H]$^{+}$), 269.0 ([{^{81}Br}M+H]$^{+}$).

Step b: 2-Amino-2-(4-bromophenyl)propanoic acid



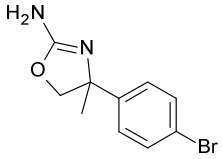
A mixture of 5-(4-bromo-phenyl)-5-methyl-imidazolidine-2,4-dione (23.3 g, 87 mmol) and aqueous sodium hydroxide solution (4M, 173 ml, 693 mmol) was stirred at 120 °C for 4 h. It was then cooled to 0 °C and the solution was brought to pH=7 by dropwise addition of hydrochloric acid (37% in water). The solid was filtered off, stirred in ethanol for 30 min, filtered off again and dried *in vacuo* to give 2-amino-2-(4-bromophenyl)propanoic acid (13.5 g, 64%) as a white solid. ^{1}H NMR (300 MHz, DMSO) δ 7.70 (d, J = 9 Hz, 2H), 7.52 (d, J = 9 Hz, 2H), 1.87 (s, 3H). MS (ISP) m/e: 242.1 ([{^{79}Br}M+H]$^{+}$), 244.0 ([{^{81}Br}M+H]$^{+}$).

Step c: 2-Amino-2-(4-bromo-phenyl)-propan-1-ol



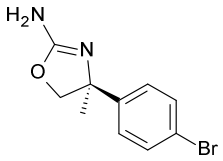
To lithium borohydride (2 M solution in THF, 140 ml, 280 mmol) was added chlorotrimethyl-silane (40.5 g, 373 mmol) slowly at room temperature. The mixture was cooled to 0 °C and 2-amino-2-(4-bromophenyl) propanoic acid (22.7 g, 93 mmol) was added in portions. The mixture was then stirred at room temperature overnight. The mixture was then cooled to 0 °C and methanol (140 ml) was added (caution!) and the mixture was then stirred at room temperature for 30 min. A solid was filtered off and washed with methanol. The combined organic layers were concentrated *in vacuo* and water (300 ml) was added. The solution was brought to pH=1 by dropwise addition of hydrochloric acid (3N in water). Ethyl acetate was used to extract non-basic material. The solution was brought to pH=12 by dropwise addition of sodium hydroxide (4N in water). The product was extracted with ethyl acetate, dried with magnesium sulfate, and the solvent was evaporated to give 2-amino-2-(4-bromo-phenyl)-propan-1-ol (12.15 g, 57%) as a white solid. ^{1}H NMR (300 MHz, DMSO) δ 7.46 (s, 4H), 4.80-4.70 (m, 1H), 3.45-3.30 (m, 2H), 1.85 (br s, 2H), 1.26 (s, 3H). MS (ISP) m/e: 230.1 ([{^{79}Br}M+H]$^+$), 232.1 ([{^{81}Br}M+H]$^+$).

Step d: 4-(4-Bromo-phenyl)-4-methyl-4,5-dihydro-oxazol-2-ylamine



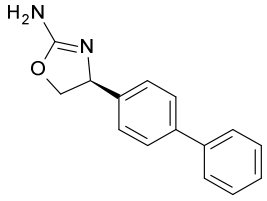
To a stirred mixture of 2-amino-2-(4-bromo-phenyl)-propan-1-ol (11.1 g, 48 mmol) and K_2CO_3 (8.0 g, 58 mmol) in (THF (180 ml) under an argon atmosphere at 0 °C was added a solution of cyanogen bromide (6.13 g, 58 mmol) in THF (100 ml). The mixture was stirred at room temperature for 18 hours, then ethyl acetate (150 ml) and NaOH solution (1 N, 200 ml) were added. The organic layer was separated and the aqueous phase was re-extracted with ethyl acetate (150 ml). The combined organic layers were washed with NaCl solution (150 ml), then dried over $MgSO_4$ and concentrated *in vacuo* to yield 12.7 g crude product which was recrystallised from cyclohexane/dichloromethane (1:1). White solid (9.06 g, 73 %); ^{1}H NMR (300 MHz, DMSO) δ 7.48 (d, J = 9 Hz, 2H), 7.35 (d, J =6 Hz, 2H), 6.00 (br s, 2H), 4.21 (d, J = 6 Hz, 1H), 3.98 (d, J = 9 Hz, 1H), 1.39 (s, 3H). MS (ISP) m/e: 255.0 ([{^{79}Br}M+H]$^+$), 257.1 ([{^{81}Br}M+H]$^+$).

Step e: (S)-4-(4-Bromo-phenyl)-4-methyl-4,5-dihydro-oxazol-2-ylamine



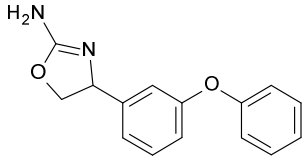
The enantiomers were separated by preparative chiral HPLC using a Chiralpak AD column and 20% EtOH/Heptane as eluent (flow 1 ml/min, 25 bar). The title compound is the (+)-enantiomer and has a retention time of 11.2 min (the (-)-enantiomer has a retention time of 7.7 min). White solid. ^{1}H NMR (300 MHz, DMSO) δ 7.49 (d, J = 6 Hz, 2H), 7.35 (d, J = 6 Hz, 2H), 6.02 (br s, 2H), 4.21 (d, J = 6 Hz, 1H), 3.97 (d, J = 6 Hz, 1H), 1.40 (s, 3H). MS (ISP) m/e: 255.1 ([{^{79}Br}M+H]$^{+}$), 257.1 ([{^{81}Br}M+H]$^{+}$).

(S)-4-Biphenyl-4-yl-4,5-dihydro-oxazol-2-ylamine (41)



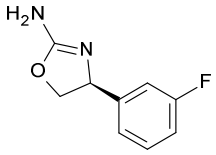
Compound **41** was prepared by reaction of rac-2-amino-2-biphenyl-4-yl-ethanol with cyanogen bromide in 53% yield according to the General Procedure, followed by chiral column chromatography (Chiralpak AD, EtOH/heptane = 20:80) to give an off-white solid, (+)-enantiomer. ^{1}H NMR (300 MHz, DMSO) δ 7.66-7.60 (m, 4H), 7.46 (t, J = 7.2 Hz, 2H), 7.37-7.32 (m, 3H), 6.11 (br s, 2H), 5.01 (dd, J = 9, 7.2 Hz, 1H), 4.55 (dd, J = 9, 8.1 Hz, 1H), 3.842 (t, J = 7.5 Hz, 1H). MS (ISP) m/e: 239.3 (M+H^{+}).

4-(3-Phenoxy-phenyl)-4,5-dihydro-oxazol-2-ylamine (42)



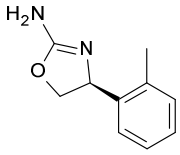
Compound **42** was prepared by reaction of rac-2-amino-2-(3-phenoxy-phenyl)-ethanol with cyanogen bromide in 53% yield according to the General Procedure to give a white solid. ^{1}H NMR (300 MHz, DMSO) δ 7.41-7.30 (m, 3H), 7.13 (t, J = 7.2 Hz, 1H), 7.03-6.98 (m, 3H), 6.91 (s, 1H), 6.86 (dd, J = 7.8, 1.8 Hz, 1H), 6.07 (br s, 1H), 4.96 (dd, J = 9, 7.5 Hz, 1H), 4.51 (dd, J = 9, 8.1 Hz, 1H), 3.781 (t, J = 7.5 Hz, 1H). MS (ISP) m/e: 255.4 (M+H^{+}).

(S)-4-(3-Fluoro-phenyl)-4,5-dihydro-oxazol-2-ylamine (43)



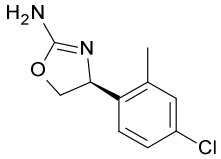
Compound **43** was prepared by reaction of rac-2-amino-2-(3-fluoro-phenyl)-ethanol with cyanogen bromide in 18% yield according to the General Procedure, followed by chiral column chromatography (Chiralpak AD, EtOH/heptane = 15:85, 1 ml/min) to give a white solid, (+)-enantiomer, retention time 12.88 min. ^{1}H NMR (300 MHz, DMSO) δ 7.40-7.02 (m, 4H), 6.15 (br s, 2H), 4.99 (t, J = 8.1 Hz, 1H), 4.53 (t, J = 8.6 Hz, 1H), 3.80 (t, J = 7.7 Hz, 1H). MS (ISP) m/e: 181.1 ($M+H^+$).

(S)-4-o-Tolyl-4,5-dihydro-oxazol-2-ylamine (44)



Compound **44** was prepared by reaction of rac-2-amino-2-o-tolyl-ethanol with cyanogen bromide in 80% yield according to the General Procedure, followed by chiral column chromatography (Chiralpak AD, EtOH/heptane = 15:85) to give a light brown solid, (+)-enantiomer. ^{1}H NMR (300 MHz, DMSO) δ 7.30 (d, J = 6.3 Hz, 1H), 7.15-7.11 (m, 3H), 6.11 (br s, 2H), 5.13 (dd, J = 9, 7.2 Hz, 1H), 4.59 (dd, J = 9.3, 7.8 Hz, 1H), 3.692 (t, J = 7.5 Hz, 1H), 2.22 (s, 3H). MS (ISP) m/e: 177.1 ($M+H^+$).

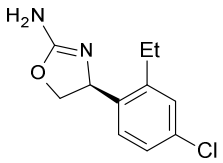
(S)-4-(4-Chloro-2-methyl-phenyl)-4,5-dihydro-oxazol-2-ylamine (45)



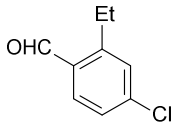
Compound **45** was prepared by reaction of rac-2-amino-2-(4-chloro-2-methyl-phenyl)-ethanol with cyanogen bromide in 31% yield according to the General Procedure, followed by chiral column chromatography (Chiralpak AD, EtOH/heptane = 10:90, 1 ml/min) to give a white solid,

(+)-enantiomer, retention time 16.69 min. ^{1}H NMR (300 MHz, DMSO) δ 7.32-7.20 (m, 3H), 6.15 (br s, 2H), 5.11 (t, J = 8.3 Hz, 1H), 4.59 (t, J = 8.6 Hz, 1H), 3.68 (t, J = 7.5 Hz, 1H), 2.22 (s, 3H). MS (ISP) m/e: 213.2 ([{^{37}Cl}M+H]$^+$), 211.1 ([{^{35}Cl}M+H]$^+$).

(S)-4-(4-Chloro-2-ethyl-phenyl)-4,5-dihydro-oxazol-2-ylamine (46)

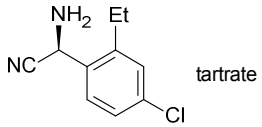


Step a: 2-Ethyl-4-chlorobenzaldehyde**(50)**



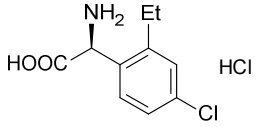
To a solution of 4-chloro-2-fluorobenzaldehyde (50 g, 315 mmol) in toluene (400 ml) were added N-butylamine (25.4 g, 347 mmol) and p-toluenesulfonic acid (1.2 g, 6.3 mmol). The mixture was heated at 110 °C for 2.5 h. After cooling, the solution was extracted sequentially with aq. $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil which was dried under high vacuum. The residue was dissolved in tetrahydrofuran (765 ml) and the solution was cooled with an ice bath. A solution of ethylmagnesium chloride (2 M, 305 ml, 610 mmol) was added slowly over 2 hours (the temperature increased slowly to 10 °C), then stirring was continued at 10 °C for 1 hour. For work-up, aqueous NH_4Cl solution was added slowly to the cooled reaction mixture (gas evolution occurred). A white precipitate was removed by filtration through a Speedex pad. Water and ethyl acetate were added for extraction. The aqueous phase was re-extracted with ethyl acetate and the combined organic layers were concentrated *in vacuo* and the residue was redissolved in 6 N aq. hydrochloric acid. The orange solution was stirred at 100 °C for 1 hour and then at room temperature overnight. The solution was then extracted with ethyl acetate, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was distilled at high vacuum (0.06 mbar, 58°C) to yield a light yellow liquid (44.2 g, 86%).) ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.22 (s, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.34 (dd, J = 8.1, 1.8 Hz, 1H), 7.29 (d, J = 1.8 Hz, 1H), 3.05 (q, 7.8 Hz, 2H), 1.28 (t, J = 7.8 Hz, 3H).

Step b: (R)-Amino-(4-chloro-2-ethyl-phenyl)-acetonitrile tartrate (**52)**



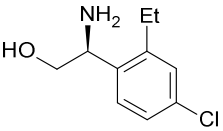
To a solution of 2-ethyl-4-chlorobenzaldehyde (26.9 g, 159 mmol) in 7 M ammonia in methanol (455 ml, 3190 mmol) at 0 °C was added trimethylsilylcyanide (23.7 g, 239 mmol) over 10 min. After stirring for 10 min, the cooling bath was removed and the mixture was stirred at 40 °C overnight. The solvent was evaporated *in vacuo* to yield the racemic aminonitrile as a brown oil. This was dissolved in a mixture of toluene and methanol (85:15, 120 ml) and added dropwise to a solution of L-tartaric acid (23.2 g, 154 mmol) in a mixture of methanol (90 ml) and acetone (12 ml, 162 mmol) at room temperature. The yellow suspension was stirred at 40 °C for 1 hour, at room temperature for 10 min and at 0 °C for 45 min. The solid was removed by filtration, washed with diethyl ether and dried under high vacuum. A white solid was obtained (31 g, 56%, 92% ee). Upon standing, another 6 g of product (83% ee) crystallised out of the mother liquor and this was collected separately. ^{1}H NMR (300 MHz, DMSO) chiral HPLC (Chiralpak AD, heptane/ethanol 90:10, λ=220 nm, 1 ml/min, rt (major) 17.49 min (minor) 15.76 min, 92% ee). ^{1}H NMR (300 MHz, DMSO) δ 7.58 (d, J = 8.1 Hz, 1H), 7.36-7.31 (m, 2H), 7.3-6.4 (br s, 4H), 5.12 (s, 1H), 4.26 (s, 2H), 2.71 (q, J = 7.5 Hz, 2H), 1.19 (t, 7.5 Hz, 3H).

Step c: (S)-Amino-(4-chloro-2-ethyl-phenyl)-acetic acid hydrochloride (**53)**



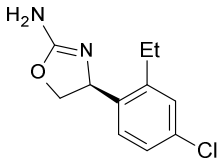
(R)-Amino-(4-chloro-2-ethyl-phenyl)-acetonitrile tartrate (59.8 g, 173 mmol, combined from various batches of 86-92% ee) was suspended in hydrochloric acid (25% aq., 230 ml) and stirred (with a KPG stirrer) at reflux overnight. The solution was cooled to room temperature, then stirred at 0 °C for 1 hour. The solid was collected by filtration and dried under high vacuum for 5 hours until a constant mass was obtained. Light grey solid (43 g, 99%), ^{1}H NMR (300 MHz, DMSO) δ 8.88 (br s, 1H), 7.45-7.36 (m, 3H), 5.16 (s, 1H), 3.1-3.6 (br s, 2H), 2.78 (qd, J = 7.5, 2.7 Hz, 2H), 1.20 (t, 7.5 Hz, 3H); MS (ISP) m/e: 214.1 ([{^{37}Cl}M-H]$^{+}$), 213.0 ([{^{35}Cl}M-H]$^{+}$).

Step d: (S)-2-Amino-2-(4-chloro-2-ethyl-phenyl)-ethanol



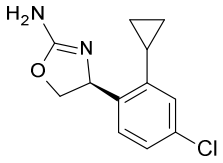
To a solution of lithium borohydride in THF (2M, 197 ml, 395 mmol) under argon were added chlorotrimethylsilane (85.7 g, 100 ml, 790 mmol) and (S)-amino-(4-chloro-2-ethyl-phenyl)-acetic acid hydrochloride (39.5 g, 158 mmol) in small portions (exothermic reaction). The mixture was stirred at room temperature for 2 h. For work-up methanol (70 ml) was added slowly with external cooling (ice bath, exothermic reaction). The resulting yellow solution was concentrated *in vacuo* and the residue was partitioned between 2 N aq. sodium hydroxide solution and ethyl acetate. The aqueous layer was re-extracted twice with ethyl acetate and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallised from ethylacetate/heptane to yield a white solid (18.9 g, 60%), ^{1}H NMR (300 MHz, DMSO) δ 7.34 (d, J = 6 Hz, 1H), 7.18 (dd, J1 = 3 Hz, J2 = 6 Hz, 2H), 4.30 (q, J = 3 Hz, 1H), 3.66 (dd, J1 = 6 Hz, J2 = 3 Hz, 1H), 3.50 (dd, J1 = 9 Hz, J2 = 6 Hz, 1H), 2.68 (m, J = 6 Hz, 2H), 1.23 (t, J = 6 Hz, 3H), MS (ISP) m/e: 200.0 ([{^{35}Cl}M+H]$^+$), 202.0 ([{^{37}Cl}M+H]$^+$).

Step e: (S)-4-(4-Chloro-2-ethyl-phenyl)-4,5-dihydro-oxazol-2-ylamine (**46**)



Compound **46** was prepared by reaction of (S)-2-amino-2-(4-chloro-2-ethyl-phenyl)-ethanol with cyanogen bromide in 63% yield according to the General Procedure to give a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, J = 8.1 Hz, 1H), 7.20-7.16 (m, 2H), 5.31 (t, J = 8.4 Hz, 1H) 4.66 (t, J = 8.6 Hz, 1H), 4.60 (br s, 2H), 3.92 (t, J = 7.7 Hz, 1H), 2.64-2.53 (m, 2H), 1.22 (t, J = 7.5 Hz, 3H), MS (ISP) m/e: 225.1 ({^{35}Cl} [M+H]$^+$), 227.1 ({^{37}Cl} [M+H]$^+$). HPLC 98.6% ee (column chiralpak-IC, 250x4.6mm, heptane/ethanol+0.2% ethylenediamine).

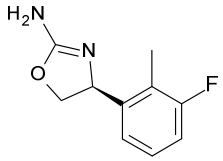
(S)-4-(4-Chloro-2-cyclopropyl-phenyl)-4,5-dihydro-oxazol-2-ylamine (47)



Compound **47** was prepared by reaction of (S)-2-amino-2-(4-chloro-2-cyclopropyl-phenyl)-ethanol (which was obtained according to the procedure described for compound **46**) with cyanogen bromide in 68% yield according to the General Procedure to give a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 8.4 Hz, 1H), 7.17 (dd, J = 8.4, 2.1 Hz, 1H), 6.98 (d, J = 2.1 Hz, 1H), 5.60 (t, J = 8.4 Hz, 1H), 4.74 (t, J = 8.6 Hz, 1H), 4.57 (br s, 2H), 3.96 (t, J = 7.7 Hz, 1H), 1.79 (m, 1H) 0.99-0.89 (m, 2H), 0.79-0.72 (m, 1H), 0.63-0.57 (m, 1H), MS (ISP) m/e:

236.9 ({^{35}Cl} [M+H]$^{+}$), 239 ({^{37}Cl} [M+H]$^{+}$). HPLC 99.3% ee (column: chiralpak-IC, 250x4.6mm, heptane/ethanol+0.2% ethylenediamine).

(S)-4-(3-Fluoro-2-methyl-phenyl)-4,5-dihydro-oxazol-2-ylamine (48)



Compound **48** was prepared by reaction of rac-2-amino-2-(3-fluoro-2-methyl-phenyl)-ethanol with cyanogen bromide in 41% yield according to the General Procedure, followed by chiral column chromatography (Chiralpak AD, EtOH/heptane = 10:90, 1 ml/min) to give a white solid, (+)-enantiomer, retention time 13.18 min. ^{1}H NMR (300 MHz, DMSO) δ 7.20-7.16 (m, 2H), 7.04-7.00 (m, 1H), 6.13 (br s, 2H), 5.16 (t, J = 8.1 Hz, 1H), 4.60 (t, J = 8.6 Hz, 1H), 3.72 (t, J = 7.5 Hz, 1H), 2.13 (s, 3H), ^{13}C NMR (300 MHz, CDCl3) 162.15, 161.25 (d, J = 243 Hz), 144.54 (d, J = 4 Hz), 127.09 (d, J = 9 Hz), 121.64 (d, 16 Hz), 121.23 (d, J = 3 Hz), 113.75 (d, J = 23 Hz), 74.24, 64.54 (d, 3 Hz), 10.40 (d, J = 6 Hz), $[\alpha]^{20}_{D}$ + 86.60° (c = 1.00, MeOH), MS (ISP) m/e: 195.1 (M+H^{+}). HRESI calculated for C10H11FN2O [M]$^{+}$ m/z 194.08554; measured m/z 194.08622.